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DEPARTMENTS

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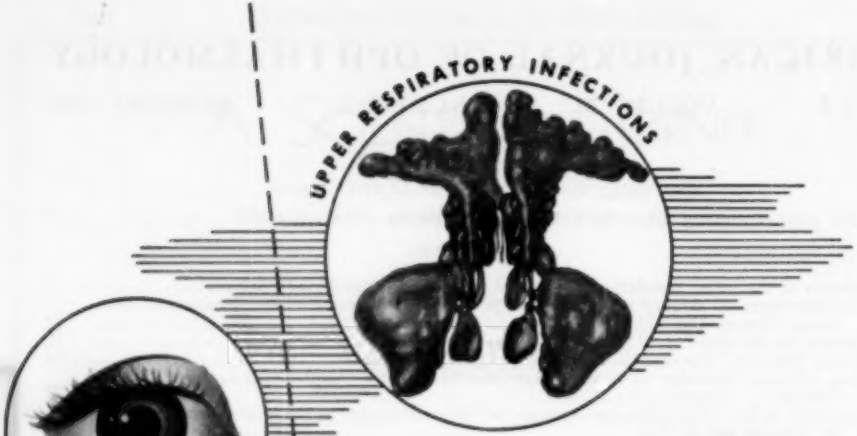

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AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 33 JANUARY, 1950 NUMBER 1

DISEASES OF THE ORBIT*

THE JACKSON MEMORIAL LECTURE

WILLIAM L. BENEDICT, M.D.
Rochester, Minnesota

It is not possible always to make a definite diagnosis of a pathologic disorder within the orbit on the basis of the clinical findings alone. The progress of a local disturbance within the orbit sometimes must be observed until definite clinical signs develop or until microscopic examination of tissue can be made. Space-occupying lesions of the orbit cause protrusion of the globe, interference with ocular motility, and sometimes disturbances of vision. These symptoms are found in a number of diseases of the orbit, but in many pathologic conditions there are no definite orbital signs by which one can clearly determine either the nature or the extent of the disease. In some systemic disorders, such as exophthalmic goiter, tularemia, and Mikulicz's disease, a gradual swelling of the eyelids appears in addition to an increase in the orbital tissues and exophthalmos. The similarity of the external signs is such as to confuse the diagnosis, which is finally made possible only through additional findings by a general physical examination.

Certain orbital complications are common to a number of general systemic diseases. Some general diseases cause specific orbital complications which are almost diagnostic. In attempting to evaluate the signs and symptoms of orbital diseases, especially in relation to local diseases of the orbit, laboratory facilities should be freely employed. Roentgenograms of the orbit should be made, and clinical pathologic tests, including examinations of the blood, are essential. In some cases, however, after all clinical data have been assembled, including the results of laboratory tests, it is not possible to arrive at a definite diagnosis and the question of whether or not to remove a specimen for biopsy arises.

It is highly desirable, of course, to arrive at a diagnosis before attempting to institute treatment for a disease of the orbit. In some cases, however, it may not be feasible to pursue a prolonged clinical investigation, and the application of roentgen or radium therapy may be begun as a therapeutic trial and as a diagnostic measure. In other cases, surgical intervention may be a means of treatment or it may be considered no more than a means of arrival at a diagnosis.

I cannot agree with surgeons who believe that it is advisable to perform biopsy routinely as a diagnostic measure and leave the decision as to surgical procedure until the result of a single biopsy is known. Removal of a specimen for biopsy with a trocar, for example, is especially bad practice. The hazard is easily understandable. When one thinks of the danger of opening into an aneurysm with consequent bleeding difficult to control or of opening into a malignant tumor that is well encapsulated, the possibility of causing surgical complications and of spreading the disease is hardly equaled by the probability of gaining useful information.

If a specimen for biopsy must be ob-

* From the Section on Ophthalmology, Mayo Clinic. Presented at the 54th annual session of the American Academy of Ophthalmology and Otolaryngology, October, 1949, Chicago, Illinois.

tained, the surgeon should be prepared to complete any surgical operation necessary as indicated by the findings or prompted by any complications that may arise as the result of removal of the specimen.

The history and the clinical findings usually afford a very strong lead toward a diagnosis, and in most instances further observation for a reasonable time may clear up what seems at first to be a rather difficult situation.

Consideration of orbital disease may be approached from two points of view: (1) The clinical signs and symptoms such as proptosis, swelling of the eyelids and orbital tissue, ocular palsy, and pain, and (2) pathologic findings on microscopic examination. For a clear understanding of diseases of the orbit, they should be classified on a clinical and pathologic basis, and the two classifications should be fitted together.

The diseases of the orbit may be clinically classified into five categories: (1) Congenital, (2) vascular, (3) neoplastic, (4) inflammatory, and (5) endocrine. For the purpose of diagnosis and treatment, almost all of the disorders and diseases of the orbit can be allocated to one or another of these groups.

Conditions brought about directly or indirectly by trauma, of course, are not considered to be orbital diseases in the sense that applies to the five named categories except in the vascular group, which includes such conditions as pulsating exophthalmos and vascular aneurysm, which may be spontaneous or the result of cranial injury, and the inflammatory diseases, which may result from infection of the orbit through penetrating injury.

In the early stages of some of the diseases of the orbit, the outstanding and sometimes the first and only signs of disease are exophthalmos with some degree of swelling of the eyelids. The character of the onset, the duration of the symptoms, and the course of development of changes within the orbit, in other words, the history of the case, may reveal nothing diagnostic, the clinical pathologic tests may not disclose any abnormality, and one may be forced to await further developments. Seldom is it wise to resort to biopsy in cases in which the clinical and laboratory findings are indeterminate.

The classification of diseases of the orbit into five categories simplifies the analysis of the signs and symptoms of the disease. Congenital diseases and disorders, as a rule, are easily recognized and are not confused with diseases of any of the other four groups. Vascular diseases and neoplastic diseases frequently are indistinguishable from each other, especially in the early stages. The greatest confusion in diagnosis arises in cases of inflammatory and endocrine disease. In these cases, the history and findings are similar and inexact, and the changing terminology probably has added to the confusion.

Congenital diseases of the orbit

In fetal life, the orbits are well formed by the seventh month. From then to adult life, the orbit almost doubles in vertical diameter, moving forward and upward, but chiefly forward. The eyeball fills the orbital cavity more completely at birth than at maturity. Congenital deformities begin early in the development of the skull and are well advanced by the seventh month.

A congenital condition believed to be due to an enlargement of the lesser wings of the sphenoid bone is hypertelorism, a congenital anomaly of the skull and face characterized by wide separation of the orbits. This is only one of the milder forms of orbital disorder that are not extremely disfiguring and disabling.

More extensive interference with development of bones of the skull results in a great variety of orbital disorders that make impossible proper function of the eyes, for in most instances the eyes themselves are also improperly developed. Microcephaly, megalocephaly, tower skull, and hydrocephalus all are congenital deformities of the skull that affect the orbit several months before birth and are not amenable to correction.

Arrested development of the eyes due to malnutrition during intra-uterine life, especially deficiency in vitamin A, has a secondary effect upon the orbit and is not amenable to treatment. A variety of congenital diseases of the eyes, such as microphthalmia and buphthalmos, are responsible for secondary changes within the orbit. These conditions, too, are self evident on examination and need lead to no confusion with conditions and diseases of the orbit that may be classified in the other four categories.

lecture last year, I described a method of analyzing the signs of orbital tumor on an anatomic basis. Three surgical divisions of the orbit are described because they have surgical implications that are based on anatomic structures (see fig. 1). The orbit is then considered in three different zones—posterior, middle, and anterior—because lesions, particularly tumors, situated in any one of these three zones tend to produce signs and symptoms which indicate their position. Trying to fit the signs and symp-

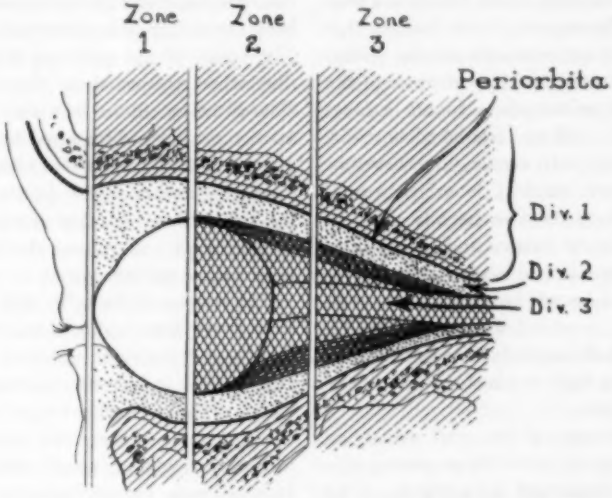

Fig. 1 (Benedict). A diagram of the orbit indicating an arbitrary division into three zones and their anatomic relation to the anatomic divisions.

Vascular and neoplastic diseases of the orbit

The greatest number of slow-growing space-occupying lesions of the orbit are neoplastic. Tumors, both primary and metastatic, are found in all tissues and in all parts of the orbit. Vascular diseases of the orbit may also come on gradually and in many ways simulate the development of an orbital neoplasm. It is well worth while to consider whether there are means of distinguishing vascular and neoplastic diseases. In the de Schweinitz

toms of a space-occupying lesion within the orbit into one of these three divisions and one of the three described zones simplifies the problem of surgical intervention and undoubtedly aids tremendously in diagnosis.

The three anatomic divisions of the orbit are: (1) Subperiosteal, (2) that between the periosteum and the muscle cone, and (3) that within the muscle cone. Tumors and space-occupying lesions of the first division may be found anywhere about the orbit. The greatest number of primary and secondary

tumors of the orbit are found in the second division, that is, between the periosteum and the muscle cone, and may be found in any of the three zones. Tumors in the third division, that is within the muscle cone, involve only the middle and posterior zones. By this arbitrary division of the orbit into divisions and zones, the probable situation of the lesion can be thought of in connection with the normal anatomy of this region and the probabilities in favor of neoplasms or vascular disease can be more readily recognized.

In the first anatomic division, that is, the subperiosteal, the commonest lesions are neoplastic and inflammatory. Bone tumors that invade the orbit are osteomas, arising within the adjacent sinuses, and hyperostosis of the orbital wall. Hyperostosis is found in cases of acromegaly, diffuse cranial dysostosis, meningioma, vascular tumor, and developmental disorders such as leontiasis ossea. The inflammatory diseases usually arise in the nasal accessory sinuses and give rise to periostitis, subperiosteal abscess, osteomyelitis, and, in case of penetration through the periosteum, to orbital cellulitis and orbital abscess. The inflammatory diseases will be dealt with more fully in consideration of the next two categories.

Vascular diseases of the orbit arising in the first division are rare. Those arising outside the periosteum and invading the orbit are easily detectable by orbital signs and may be revealed in roentgenograms with the aid of radiopaque substances if necessary. Pulsating exophthalmos resulting from arteriovenous aneurysm within the cavernous sinus and a proptosis with congestion of the orbit and choked disc found in cavernous sinus thrombosis are examples of this type of lesion.

What is probably the most common neoplasm entering the orbit through the periorbita, that is from Division 1, is cranial meningioma. In most of the cases of orbital meningioma the tumor originated outside the orbit and the characteristic finding is a thickening of the sphenoidal ridge along the roof of the orbit, frequently referred to as "osteoma," but properly called "hyperostosis."

The appearance in the roentgenogram is that of a localized thickening of the roof of the orbit, and it occurs in such a high percentage of cases as to become a major diagnostic factor. It must not be forgotten, however, that all extraorbital meningiomas do not give rise to hyperostosis and that there are other diseases besides meningiomas that will give rise to a similar thickening of the bone. It is well known that the development of a hemangioma or any pulsating lesion that lies near bone may give rise to changes in the bone consisting of hyperostosis or dysplasia. The bones of the orbit are likely to become thin when subjected to the pressure of a slow-growing tumor or a cyst. The appearance, therefore, of hyperostosis in the roentgenogram of an orbit that contains a space-occupying lesion is not in itself diagnostic but will indicate a lesion of vascular or neoplastic origin; therefore, the lesion falls in one of these two categories.

The lesions of the orbit that arise in Division 1 are found almost exclusively in the middle and posterior zones of the orbit, except for the inflammatory group of diseases which originate in the frontal sinus and the true osteomas of the orbit that arise usually in the ethmoidal cells and occasionally in the frontal sinus. True osteomas of the orbit are always extraperiosteal. They are unmistakably represented in roentgenograms and do not constitute a problem in diagnosis.

Within the second anatomic division of the orbit, that is, the division between the periosteum and the muscle cone, occur the greatest number and the greatest variety of space-occupying lesions of vascular and neoplastic origin. Lesions of the middle division that occur in the posterior zone, that is, in the posterior third of the orbit, are characterized by direct proptosis. As a result of pressure on the optic nerve, they cause a diminution of visual acuity or scotoma in the visual field. In this section of the orbit are found the greatest number of endotheliomas, most of

which are meningiomas from without the orbit that make their way through the optic foramen or directly through the orbital roof.

A great variety of tumors have been found in this division of the orbit, many of which are metastatic but most of which are primary. The most common and, of course, the most characteristic features of such neoplasms are proptosis, displacement of the eyeball, and swelling of the eyelid. The onset of proptosis is not necessarily an indication of the time when a tumor begins to grow. The displacement of the eyeball is not necessarily an indication of the situation of the tumor within the orbit in relation to the eyeball. A slow-growing lesion, either a tumor or aneurysm, may acquire considerable size, up to the size of the globe itself, before producing appreciable proptosis. Such lesions tend to find a place for themselves within the orbit where resistance to growth is minimal, and the bulk of the tumor may be a considerable distance from its origin.

Hemangioma of the orbit is the most commonly found tumor of vascular origin in this division, and, because of the great variety in the size, shape, and density of this tumor, one may not be able to distinguish a vascular tumor such as hemangioma from a solid tumor, a sarcoma, for instance, by the physical finding alone. There are, however, some signs of vascular tumor that are very helpful when present.

Vascular aneurysms and some types of hemangiomas vary considerably in size during the process of development owing to the accumulation of blood cysts which undergo thrombosis and absorption. As a result of change in the size of the tumor, a fluctuation in proptosis will be noted, oftentimes to the point of complete disappearance of all signs of intraorbital disturbance. The history of recurrent exophthalmos is always suggestive of vascular tumor with thrombosed aneurysm but is not necessarily diagnostic. Exceptions to the rule, however, are rare. In most cases, fluctuating proptosis or intermittent exophthalmos can be attributed to intraorbital vascular lesions in this middle division.

The large vascular spaces in hemangiomas may become pinched off so that blood no longer circulates, giving rise to what is called a "thrombosed aneurysm." The blood in the thrombosed areas breaks down into a thin, colored fluid which escapes through the wall of the aneurysm and permeates the tissues of the orbit. A bluish discoloration of the skin of the eyelid is not uncommon as the result of the disintegration of a thrombosed aneurysm, and when this discoloration appears in the case of an orbital space-occupying lesion with fluctuating proptosis, the findings are practically pathognomonic.

Whenever it is possible to rule out the presence of a vascular lesion in the middle division of the orbit and the middle and posterior zones, the signs of a space-occupying lesion point very definitely toward the presence of a neoplasm. The nature of the neoplasm cannot, of course, be determined except by pathologic examination, but its size and situation can be inferred from the findings on examination.

Roentgenograms frequently will reveal the presence of a soft tissue tumor, and, in cases in which the findings are indefinite, such a tumor may be made to appear more clearly in the roentgenogram by the injection of air into the orbit. This procedure, done under local anesthesia, is painless and harmless when only a neoplasm is present but has dangerous potentialities if used indiscriminately in all cases of orbital disease with exophthalmos. The injection of radiopaque substances into the blood stream in an effort to delineate lesions of the orbit more clearly in the roentgenogram has been an unsatisfactory procedure and should be employed only by those who are fully familiar with the technique and fully equipped to take best advantage of the findings.

Spontaneous vascular aneurysms within the orbit may occur at any age. Inasmuch as many of them are found in children, it is believed that a congenital lesion which de-

velops and expands with age is responsible for most of them. The most significant findings in these venous aneurysms are their intermittent character, sudden onset, sudden remission, and gradually increasing severity. Venous aneurysms particularly have a tendency to spread, as is well exemplified by the recurrences that one encounters after surgical excision of what seems to be an ample amount of vascular tissue. The aneurysms have a tendency to become thrombosed and to form a network of fibrous masses on contracted fibrous tissue which may become partially calcified and made detectable by roentgenologic examination.

Tumors and space-occupying lesions that lie within the muscle cone (the third division) are situated in the middle and posterior zones of the orbit. The distinguishing features of lesions usually found there are proptosis without lateral displacement of the eye, wrinkling of the retina due to pressure upon the posterior wall of the globe, choked disc, visual loss, and scotomas. The tumor most common in the muscle cone springs from the optic nerve or its sheath, that is, a neurofibroma, glioma, or endothelioma.

The most favorable surgical approach to tumors situated within the cone is by the transcranial route. In any case of vascular space-occupying lesion within the posterior two thirds of the orbit, surgical intervention through the outlet from in front should be avoided. This is especially true of aneurysms. The transcranial approach permits visual dissection of aneurysmal vessels that usually are affected as far as the wall of the orbit. They can only be removed and properly ligated under direct inspection.

The exophthalmos that occurs in such cases frequently is the result of disturbances of circulation and edema of the orbit, and exophthalmos will persist after the diseased vessels have been entirely removed. As the circulation is already somewhat impaired, roentgen therapy should not be employed as it is likely to embarrass the circulation further. The end result of roentgen therapy in such cases is not predictable. There is some question as to whether roentgen therapy should be used in the treatment of vascular tumors of the orbit, particularly vascular aneurysms, except in cases in which surgical treatment is contraindicated.

The large number of tumors of various types that have been described have in common such signs as exophthalmos, lateral displacement of the globe, and swelling of the eyelids; so, it is possible on clinical grounds to postulate the type of the tumor present in the middle zone and middle division of the orbit before operation is performed. There is no real necessity for making a differential diagnosis before removal of the tumor, for once a tumor is encountered it should be totally removed if possible with a minimum of trauma to surrounding tissues.

Investigation should be centered not so much on the histologic type of tumor as on whether or not a tumor actually is present and whether or not the signs of orbital lesion can be attributed to some other cause. The most common diseases simulating tumor of the orbit are low-grade inflammatory granulomas, lymphatic diseases, and the orbital complications of diseases of the glands of internal secretion.

The overlapping of the signs and symptoms of vascular and neoplastic disease and inflammatory and endocrinous diseases is rather wide and contains all the elements of diagnosis to such an extent that the term "pseudotumor of the orbit" is used almost as frequently as any other in accounting for exophthalmos and the associated disturbances of vision.

Pseudotumor is not a diagnostic term and is not a clinical entity, but the use of this term is justified on the basis of statements made by Birch-Hirschfeld, in the Graefe-Saemisch Handbuch, second edition, 1910. Birch-Hirschfeld's classification of pseudotumors has been followed by most writers in reporting such cases, although many authors have been negligent in reporting their cases in such a way that they can be allo-

cated to one of the three types described.

Birch-Hirschfeld drew attention to the inflammatory character of tissue removed from the orbit in cases of proptosis and blindness in which the clinical data suggested the presence of a neoplastic lesion. He described an inflammatory disease of the eye that can only be verified by microscopic examination, but as the field is rather wide he classified pseudotumors into three groups.

In cases of tumors of Group 1, the clinical syndrome is that of benign of malignant neoplasms but recovery occurs spontaneously or after administration of drugs such as potassium iodide, mercury and quinine. In cases of tumors of Group 2, the diagnosis of orbital tumor is made on the basis of the clinical findings but a tumor is not found when the orbit is opened. In cases of a tumor of Group 3, a tumor is found at operation but on microscopic examination it is found to consist of chronic inflammatory tissue.

Most of the so-called pseudotumors which have been reported in recent literature fall in Group 2. Explanation of the exophthalmos in such cases has included such conditions as malignant hypertension, orbital cellulitis, exophthalmos of thyroid disease attributed to a thyrotropic hormone of the pituitary body, syphilis, tuberculosis, vascular aneurysms, and small tumors that were missed on surgical exploration of the orbit but which later became evident.

The category of inflammatory diseases of the orbit is thus seen to include both chronic and acute conditions, some due to unknown infection or unknown disease. The symptoms of orbital tumors that are due to disturbances of the endocrine glands are related both to neoplastic and to inflammatory causes. For example, the exophthalmos of acute hyperthyroidism is principally inflammatory and in many cases can only be identified through additional physical findings. In cases in which additional clinical findings are contradictory or not corroborative, the confusion is greatly confounded. The two categories, inflammatory and endocrinous diseases, may be considered together as against vascular and neoplastic diseases, as a crude method of discrimination or differentiation. The finer points of distinction between inflammatory and endocrinous diseases require further consideration.

Inflammatory and Endocrinous diseases of the orbit

At the outset, it should be understood that the difference between acute and chronic diseases of the orbit is made not so much on a basis of duration of the symptoms as upon the evidences of inflammation such as pain, congestion, degree of swelling of the lids and orbital tissues, and the loss of visual function. Acute inflammatory lesions of the orbit are produced largely by disease of the nasal accessory sinuses, especially the ethmoid cells in children, the frontal sinuses and the maxillary sinus in adults.

Primary acute inflammation arises from foci of infection, from constitutional diseases such as typhoid fever, rheumatism, tuberculosis, and syphilis. Severe acute orbital disease has been found in association with tularemia, coccidiosis, tick fever, rickettsial diseases, and some of the virus diseases. There is no reason to believe that the orbit is immune from any of the infectious diseases that are manifested elsewhere in the body and known to be due to any type of disease-producing organisms.

Orbital cellulitis, periostitis, and orbital abscess which complicate diseases of the paranasal sinuses are most often found to be due to the Streptococcus and Staphylococcus, both pus-producing organisms which produce disease, as a rule of short duration. Complete and permanent recovery follows adequate drainage and a comparatively short course of therapy.

The occurrence of acute orbital cellulitis in infants due to primary disease of the ethmoid cells has been well established in spite of the well-known fact that the sinuses are incompletely developed. Surgical intervention is very seldom necessary in cases of

acute orbital cellulitis in which the patients are small infants. In very young infants the disease usually is cured spontaneously by rupture and drainage through the nasal wall.

Acute orbital cellulitis in adults frequently leads to the formation of an abscess. If allowed to persist, the abscess usually points in the upper eyelid somewhere along the superior rim of the orbit. The abscess forms in the dome of the orbit between the muscle cone and the periosteum in the anterior third of the orbit. Consequently, the most effective way of draining such an abscess is by an incision made through the upper lid at the middle of the upper orbital rim and extended backward along the roof of the orbit into the middle zone. Incision in this position endangers none of the nerves, vessels, or other important structures about the superior nasal quadrant of the rim of the orbit. It provides the most adequate drainage, relieves complications, and prevents consequent disfigurement. Incisions through the cul-de-sac, particularly in the region of the inner canthus, should be studiously avoided.

The so-called inflammatory diseases of the orbit, aside from the infectious processes resulting from penetrating injuries and extension within the orbit of disease from the nasal sinuses, may be considered complications of a systemic infection. Tularemia is a striking example. Such disease is comparatively rare and the cause may be overlooked unless specific tests are made. In the first four cases of orbital complications of tularemia seen at the Mayo Clinic, the patients were definitely ill with fever, malaise, and pain. In the fifth case the patient had no general or neurologic symptoms but had had a unilateral proptosis and low-grade orbital cellulitis for several weeks. The cause of the disease was only revealed by a hematologic examination made by an alert physician after the patient had been dismissed from the clinic to await further developments.

The cases of chronic inflammatory pseudotumors of Birch-Hirschfeld's Group 2 and Group 3 which were reported by Benedict and Knight in 1923 were seen at the clinic within a period of three years, but in the following 25 years only two additional cases were encountered. The cause of the condition is not known. In none of the cases was the clinical course of long duration. Symptoms appeared about three months before they became severe enough to cause the patient to seek medical advice.

In several cases, the symptoms began insidiously and fluctuated for some time, and then became severe and constant. At operation the retrobulbar tissue was found to be studded with groups of lymphocytes resembling follicles, with an outer ring of plasma cells. The endarteric changes and the absence of all signs of malignant growths formed the characteristic picture. All cases were thoroughly investigated for the presence of syphilis but history, clinical findings, and serologic tests did not disclose any evidence of this disease and a pathologist noted for his knowledge of the pathology of syphilis reviewed the slides and declared that the histologic picture could not be attributed to syphilis. That the disease was due to bacterial or viral infection seems plausible, owing to the character of the onset, the short duration, and the pathologic findings.

One other disease of the orbit having a similar onset and clinical findings has recently been encountered at the clinic. It also exemplifies the unusual benign orbital lesions which produce signs that indicate the presence of a malignant tumor. I have operated in two cases of solitary sarcoid of the orbit in which a palpable tumor protruded around the margin of the orbit in the superior temporal quadrant and invaded the lower eyelid. In one of these cases, the operation was performed in 1926; in the other case, it was performed in 1948.

Both of the patients were elderly women whose general health was good. The symptoms of orbital involvement were exophthalmos, swelling of the eyelids, and a solid mass which had been present at the temporal rim for about four months before the patients

sought medical assistance. In both cases, the preoperative diagnosis was orbital tumor, which, probably because of its situation, was believed to be an adenocarcinoma. In the first case, a diagnosis of tuberculosis of the orbit was made at the time of operation; in the second case, a diagnosis of sarcoid of the orbit was made.

The clinical and pathologic findings were similar in both cases. A number of pathologists who reviewed the histologic sections agreed that both tumors were sarcoids. In the second case, careful bacteriologic examination of the surgical specimen did not disclose the presence of Mycobacterium tuberculosis. Tumor tissue was implanted into animals, but subsequent examination of the animals did not reveal any evidence of tuberculosis. After the operation, the patient in this case was reëxamined carefully, but evidence of tuberculosis or sarcoidosis elsewhere in the body was not found. The patient in the first case was well in 1948, 22 years after removal of the tumor. The sarcoid has not recurred in either of these cases.

A diagnosis of pseudotumor frequently has been made in cases of exophthalmos in which an exploratory operation on the orbit does not reveal any cause for the exophthalmos. In some cases, an exploratory operation may fail to disclose a small tumor situated in the posterior part of the orbit. In some cases, a cyst or a thrombosed aneurysm of the orbit may collapse as a result of rupture of its walls and may not be identified at the time of operation. I have observed cases in which this occurred.

In cases of malignant hypertension associated with exophthalmos and choked disc, failure of an exploratory operation on the orbit to disclose a tumor has resulted in a diagnosis of pseudotumor. In such cases, the pathologic examination of the tissues involved does not disclose the characteristic picture described by Birch-Hirschfeld; therefore, such cases should not be classified as cases of chronic inflammatory pseudotumor.

Although the exophthalmos of goiter produces a characteristic pathologic picture that should prevent confusion in diagnosis even in the absence of general clinical findings, some authors fail to make a distinction on the basis of the pathologic findings and have attempted to classify exophthalmos of goiter in the group of chronic inflammatory pseudotumors. There are no real points of similarity in the pathologic findings to warrant such a grouping. The attempt to explain proptosis of goiter by assuming activity of a thyrotropic hormone is a current endeavor which should be only tentatively accepted until a better explanation is proposed. Physicians are often puzzled by exophthalmos in cases in which the basal metabolic rate has never been known to be above the normal range or has consistently been below normal in the absence of a history of symptoms of toxic goiter.

There is good reason to doubt that the quiet, noncongestive exophthalmos is inaugurated by the pituitary-produced thyrotropic hormone alone without initial changes in the thyroid gland. The signs of thyrotoxic goiter may be overlooked when they are mild and of short duration. We do not yet know how much disturbance of the thyroid is necessary to produce exophthalmos or whether the pituitary body plays a primary or secondary role in its production. In many cases of dysthyroidism, there are no orbital complications whatsoever. The mechanism of exophthalmos of dysthyroidism is not yet clear, and the etiologic role of the pituitary body has not been satisfactorily demonstrated.

If, through mistaken diagnosis or a desire to establish a diagnosis, the orbit is explored and nothing is found to explain the exophthalmos, a specimen of an ocular muscle should be removed for biopsy. The pathologic findings of exophthalmic goiter are typical and occur early in the course of the disease. They are found so regularly that, in the absence of general clinical findings of hyperthyroidism, the diagnosis may be admitted. The absence of the usual finding in

the orbital muscles must be taken as a sign that dysthyroidism was not a factor in the production of exophthalmos.

There are no other endocrinous diseases of the orbit that are so well described as those resulting from disorders of the thyroid gland and the pituitary body. There is no established connection between disease of the orbit and allergy, but that there are orbital swellings caused by an allergic disturbance has been claimed by some authors with considerable justification. Angioneurotic edema of the orbit with exophthalmos is a rare condition which may be attributed to endocrine disturbance or to allergy. The symptoms are usually severe pain which is situated in the back of the neck, top of the head, back of the globe, and extends to the jaws. Exacerbation of the pain occurs at irregular intervals. The symptoms are variable in severity and occurrence and are difficult to control. Roentgen therapy produces the best results.

Tumors of the orbit of lymphatic origin are oftentimes confused with neoplasm and with goiter. The exophthalmos and the palpebral complications of Mikulicz's disease are due to masses of lymphatic cells that simulate a tumor and the chronic inflammatory diseases of the orbit described by Birch-Hirschfeld. The chief finding that clinically distinguishes this type of exophthalmos from that of goiter is the presence of masses in the eyelids that can be palpated in Mikulicz's disease, whereas the swelling of the lids in goiter is smooth and uniform. The masses in the lids and the orbit occurring in Mikulicz's disease readily disappear as a result of roentgen therapy while the exophthalmos of goiter is not immediately altered by roentgen rays.

With all our means of clinical and pathologic examinations we may not be able to make a diagnosis of orbital disease in many cases of exophthalmos. When there are no definite clinical criteria, the diagnosis must await pathologic examination. However, there may be reasons for deferring exploration, and biopsy may not be feasible.

In a case in which the findings are indefinite and there is no immediate danger of visual loss and no pain or other serious symptoms, I would strongly urge the application of roentgen rays as a diagnostic and therapeutic measure. I have seen many cases in which orbital disease with exophthalmos has been cured by roentgen therapy, and I am not chagrined at my inability to establish a definite diagnosis in such cases.

The interests of the patient come first, and in most instances the diagnosis will become evident eventually, probably by inference, probably by delayed symptoms, but if the diagnosis is never established no harm has been done. In the light of our knowledge of diseases of the orbit, our modern methods of diagnosis and the treatment of local and systemic diseases by modern methods of irradiation and chemotherapy, there would seem to be little excuse for orbital exploration for the sake of curiosity.

Seldom does a disease of the orbit require emergency treatment. A period of watchful waiting in cases in which the diagnosis is doubtful is nearly always justified, and surgical intervention, as a rule, may well be deferred until satisfactory proof of diagnosis is at hand or until definite damage to some important structure seems imminent.

Mayo Clinic.

THE DEPENDENCE OF SURGERY ON PHYSIOLOGY*

With special reference to the treatment of glaucoma

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It is a truism to which we all pay lip service that a thorough understanding of disease can only be based upon a sound knowledge of normal function, that sickness can only be interpreted in terms of disordered health, and that our therapeutics—whether in medicine or surgery—must be the handmaid of physiology. That our conduct as surgeons is not always modelled on this truth is undeniable—but understandable when we remember that our knowledge of the normal is in most cases very perfunctory and in many cases almost completely absent. And when we are confronted with patients with clamant symptoms demanding immediate relief, we would be failing in our duty if we did not employ every means available to us even though we know some of these means are often empirical or based on premises we may suspect to be wrong. There is, however, I think, a tendency among surgeons who are zealous in their craft, sometimes for that reason the most able technically, to forget the empiricism of their methods, to think that by relieving a symptom they have cured a disease and, consequently, to suffer disappointment because, despite their efforts, the more deeply-seated disease process goes on.

In ophthalmology the tendency is exemplified in concomitant squint. The obvious fault is misalignment of the eyes, the obvious cure is mechanical restitution of the alignment; but, unless the cause of the deviation is sought in some underlying disturbance of the normal mechanism of binocular vision and corrected, whether it be an amblyopia from ametropia or the development of abnormal correspondences or other cause, the condition tends to relapse; amblyopia or suppression persists so that a result which is cosmetic only and not curative is obtained, for a cure can only imply the restoration of binocular vision with two normally functioning eyes.

Similarly in retinal detachments, a great majority of cases are due to the mechanical tearing of the retina by trauma or degenerative processes and these are usually reposed by mechanical occlusion of the tear; but other cases occur wherein the hole is due to an active disturbance of the choroid and in these the same mechanical interference may result in the catastrophe of a massive choroidal reaction, a pouring out of exudate, sometimes a further tearing of the retina and usually the conversion of a partial into a more complete detachment.

The most important example of this tendency to adopt an operative technique which mechanically relieves a distressing and clamant symptom and leaves the underlying malady unaffected is, however, seen in the general views which find expression today in the treatment of glaucoma.

A survey in retrospect of the history of this disease is interesting. Although the word appears in the Hippocratic Aphorisms and in the works of Galen and the other writers of the early Christian epoch and was used to describe blindness coming on in advanced years unassociated with cataract, hardness of the eye was at that time not observed; and although it was mentioned by such writers as the Arabian Sams-ad-din in the 14th century or the itinerant English oculist, Richard Banister, in 1622, it is not until the writings of the great and astute Scottish clinician, Sir William Mackenzie, in 1830, that we find an adequate description of the disease wherein a cardinal role was ascribed to raised tension.

With the introduction of the ophthalmoscope and the description of a primary dis-

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ease characterized by raised tension and cupping of the disc by von Graefe in the 1850s, hypertension was universally accepted as the central feature of glaucoma. In 1857, von Graefe found that, after performing an iridectomy on a staphylomatous eye, the staphyloma receded; he assumed that this was due to a lowering of the ocular tension and applied the same technique to glaucomatous cases with results as dramatic as are to be found in any branch of surgery.

The introduction of this operation, together with pathologic studies showing obstruction of the angle of the anterior chamber as demonstrated by Max Knies and Adolph Weber in Germany in 1876, and the physiologic researches of Priestley Smith in 1879 in England, concentrated the whole of professional thought almost to the exclusion of anything else on the conception of a raised tension caused by a hindrance to the drainage of the intraocular fluids.

It is true that there were voices crying in the wilderness. Since the time of von Graefe himself, and more particularly of Schnabel in 1892, the occurrence of glaucoma without raised tension was claimed; but under pressure from popular opinion even von Graefe recanted from his opinion. The apparent lack of tension in many cases has been variously ascribed to its intermittent occurrence so that it may be missed on clinical examination, to its being masked on tonometric readings by increased scleral rigidity, or to weakness of the lamina cribrosa so that excavation of the optic disc would readily occur, a normal tension thus acting as if it were pathologically raised.

Despite the propagation of innumerable theories as to an ultimate cause of the disease, the consensus of ophthalmologic opinion for almost a century has been practically unanimous in insisting that the essential feature of glaucoma was raised tension; its immediate local cause, an embarrassment of drainage; and its adequate treatment, a measure by drugs or operation to improve the drainage.

Recently this train of thought has received support from gonioscopic observations on the width or narrowness of the angle of the anterior chamber and the blood content of Schlemm's canal and from studies of the behavior of aqueous veins; thereby it is suggested that a difficulty or constriction to the outflow of the intraocular fluid is a characteristic, and possibly the fundamental cause, of glaucoma.

If the be-all and end-all of glaucoma resided in a raised tension and the raised tension itself were dependent upon the width of the angle of the anterior chamber or, indeed, the efficacy of drainage of the intraocular fluids, then surely the anxieties of five generations of ophthalmologists and the tragedy of blindness that has overtaken countless numbers of their patients could be mechanically relieved by sufficiently enthusiastic surgery.

It is my submission that a raised tension is merely a complication occurring in a more fundamental disease—or, more accurately, in a congeries of disease conditions—and that the configuration of the angle of the anterior chamber—whether anatomically or pathologically determined—merely a feature which aids the incidence and may increase the drama of this complication. That practically the whole of our thoughts and energies have been concentrated almost exclusively on the aspect of drainage—important though it may be—explains the undeniable fact that, in comparison with other diseases dependent upon a mechanical maladjustment amenable to surgical correction, the prognosis of glaucoma, taken as a whole, is bad.

I propose to consider glaucoma as divisible into the two categories which I think have a fundamental etiologic importance—congestive and noncongestive. Congestive glaucoma is an ocular malady the fundamental cause of which is a vascular instability, often, it is to be noted, not limited to the eye, the unstable phase being characterized essentially by vasodilatation, increased capillary permeability, and edema. The eye, however, has

a peculiar physiologic control of its vascular system by axon reflexes which magnify such a reaction beyond ordinary bounds. By these reflexes, local circulatory events are magnified so that they readily become generalized throughout the whole uveal tract, and, in fact, may be relayed, again by nervous action, to cause a vasodilatation in the other eye. It follows that a small source of irritation which in other organs would have a slight effect, may lead to a major and widespread circulatory crisis in the eye.

We know some of the factors which may cause this instability of the capillary circulation—inflammation, trauma, the irritation of a dislocated lens, venous obstruction, and so on: we can with considerable justification designate these cases as secondary glaucomas. In the majority of cases we do not know the cause. We may surmise that into the etiology there may enter, either singly, successively, or in combination, such factors as neurohumoral anomalies, an upset in the neurovegetative balance between the sympathetic and the parasympathetic systems, endocrine dyscrasias, or the multitude of factors, physical or psychosomatic, especially those endowed with emotional tone, which are integrated in the thalamus and hypothalamic region.

To this extent some cases of glaucoma—like nonrenal hyperpiesia, gastric ulcer, or thyrotoxicosis—may be classed as a stress disease. To these general causes we may add local factors becoming effective in the eye itself; but so long as all of these remain unknown we are wise to classify all these cases in the meantime as primary congestive glaucomas.

Whatever the ultimate cause—whether it is known as in the secondary glaucomas, or still unknown—the local pathology is clear. Capillary dilatation leads to increased permeability, stasis, and local edema, and often to an increased tension in the eye. Structural considerations, however, may bring more drama into the picture. Here the congestion and edematous swelling of the ciliary body may force the iris against the cornea; repetition of this process in subsequent episodic attacks results in the formation of an increasing number of synechias; or an unusually severe degree of congestion and swelling may obliterate the angle completely and an acute strangulating crisis of tension results. If the angle of the anterior chamber is narrow, this culmination may occur early; if it is wide, the disaster may be correspondingly delayed. But while this is a common story it is by no means invariable, for gonioscopy shows that an equally acute and strangulating attack may occur, due presumably to vascular engorgement acting alone, when the angle is demonstrably open.

It is important to realize in the first place that the mechanical blockage of the angle by total annular synechias does not necessarily abolish drainage of the intraocular fluid. Reabsorption will undoubtedly occur throughout the venous capillaries of the iris and the ciliary plexus of veins and, even though the angle is seen gonioscopically to be closed, intraocular fluid may be observed draining away in the aqueous veins.

Nor do the operations we undertake for the relief of the condition invariably act by the restitution of mechanical drainage at the angle. Everyone is agreed that in the early stages of the disease a small peripheral iridectomy is an efficient and permanent prophylactic measure; and no one suggests that such an operation with its firmly healed cicatrix provides a permanent and adequate drainage mechanism. Gonioscopy shows that the basal iridectomies practised in acute glaucomas are seldom truly basal and frequently there is no evidence of a filtering scar. Similarly after an iridencleisis or a trephining operation the angle can be seen to have become closed again, and a flattened, adherent, scleroconjunctival scar disproves the persistence of drainage at this point.

It seems to be obvious that, although the establishment of local drainage is undoubtedly a factor of no small importance, and sometimes of crucial importance, in providing a

safety-valve which forestalls or controls a future crisis or compensates for a chronically raised tension, the primary effect of these operations in many, if not most, cases is explained more rationally by a modification of the circulation of the anterior uvea, possibly by the inhibition of axon reflexes so that the abandon of their reactions is controlled, than by the mechanical establishment of channels for drainage.

In the same way in hypertensive iridocyclitis, if the uveal congestion and edema can be adequately controlled by alleviation of the causal inflammation, the ocular tension may fall and remain down even in the presence of total annular synechias.

In all cases of congestive glaucoma, whether primary or secondary it does not matter, the primary lesion is vascular congestion; treatment should firstly be the control of that congestion; the state of the drainage channels or the configuration of the angle is secondary; peripheral synechias are the result of tension, not its cause. An acute attack of congestive glaucoma can occur in the presence of an open or closed angle, and, although a macroscopic drainage channel must always be a valuable asset as a cushion or safety-valve, the tension of the eye may well be normalized in the absence of visible drainage through an operative cicatrix and maintained at a high level in its presence.

Simple glaucoma, on the other hand, presents a completely different disease-picture. There is no evidence of vascular congestion or episodic events; on the contrary, a slowly progressive and insidious process characterized typically by a triad of symptoms—field defects, cupping of the disc, and raised tension—develops into an absolute stage when complete blindness is the most frequent result. If I were to be sufficiently bold to generalize on a subject about which I—or anyone else—knows little, I would say that it is a disease the essential feature of which is an inadequacy of the ocular circulation characterized by a lack of adaptive accommodation in the small vessels and a nutritional sclerosis of important tissues in the eye.

It may be that the cause of the loosening of vascular control is a structural lesion, itself of the nature of sclerosis, for this is a constant feature of such eyes as have come to pathologic examination. On the other hand, the changes may be functional: we do not yet know.

There are, however, some facts which we do know. In the first place, a significant number of patients with chronic simple glaucoma have a general vascular instability both in the general blood-pressure (which need not be high) and in the local peripheral responses to stimuli. In the second place, a feature of the eyes of such patients, particularly at an early stage of the disease, is not so much a rise of tension as a distortion and exaggeration of the normal diurnal variation of tension. We are not certain of the ultimate cause of the normal diurnal variation of tension, but the evidence is strong that it is due to rhythmic circulatory changes. In simple glaucoma the base pressure of the eye may remain normal or nearly so, but the variations run riot and the tension may rise, regularly or irregularly, to heights above the base pressure of 20 mm. Hg or more in an ascending phase, to fall again in a descending phase to the normal. At other times the pressure remains high on a level which may or may not show irregularities.

There is much evidence, however, that the local vascular condition varies fundamentally in the two phases. Tests of fluorescein permeability indicate a great variation in the flow of blood through the capillaries in this disease. In the normal eye the rate of the passage of fluorescein through the capillary walls follows a regular standard curve; in the glaucomatous eye the permeability is usually greater and there are sudden and unexpected variations.

Among the provocative tests which lend themselves to the study of this problem, the lability test and venous-pressure test are usually positive during the ascending phase and negative in the descending; that is, if an

artificial rise of pressure is provoked, the rise is pathologically accentuated in the ascending phase, negligible in the descending phase. The same applies to the bulbar pressure test when the eye is subjected to a standard external pressure: in the ascending phase the rise in ocular tension is often abnormally high; in the descending phase no rise may occur.

This difference in response during the two phases, much of our knowledge of which is due to the work of Thomassen, has not been adequately recognized up to the present and is, I think, responsible for much of the divergence of views regarding the value of these provocative tests. However that may be, the evidence indicates that, in the rising phase of tension, the ocular capillaries lack some control which is normally present, an instability which does not persist in the descending phase.

It is to be noted that the same variation in the response to provocative tests is seen, muted in degree but the same in kind, after miotic treatment or after a drainage operation. This would seem to indicate that, despite the control of tension by the establishment of drainage, the same fundamental instability exists. The operation has not abolished it, but has only mitigated or nullified its effects so far as the tension of the eye is concerned.

So far as I can see at present, the circulatory changes characteristic of the rising phase of tension are a lessening of blood-flow through the capillaries with a raised hydrostatic pressure and a raised venous pressure—a state which is unstable, for dilatation is readily elicited on stimulation; the descending phase is characterized by a capillary dilatation with perhaps the opening out of new capillary districts, an increased circulatory flow, and a fall in venous pressure.

It has frequently been remarked that it is usually difficult on inducing venous congestion to force blood back into the canal of Schlemm in chronic simple glaucoma. It is also said that it is difficult to force aqueous out of the eye in this disease into the aqueous veins and that a positive glass-rod or aqueous-influx phenomenon is not obtained in these veins. It has been argued, particularly by Ascher and Goldmann, that these observations indicate an organic obstruction in the drainage channels of the eye; and on this basis the argument sounds conclusive.

I do not think, however, that things are as simple as that. In my clinic we find it possible to fill Schlemm's canal with blood in 20 percent of cases of simple glaucoma by inducing venous congestion with the gonioscope. Our observations agree that the aqueous-influx phenomenon is not seen in glaucomatous eyes during the ascending phase when the ocular tension is rising but we find that it is frequently seen during the descending phase.

We have observed one case of typical chronic simple glaucoma in which not only could the canal of Schlemm be filled with blood on inducing congestion of the eye but an aqueous-reflux phenomenon could also be obtained in an aqueous vein. In this case there was easy two-way traffic either to blood or to aqueous throughout the drainage channels.

We agree with Ascher and Goldmann that, in the normal eye any single aqueous vein preserves its characteristic of showing an aqueous- or blood-influx phenomenon over periods of years: this is a constant feature of each individual vein. But in glaucoma, the phenomenon varies: In a rising phase of tension, there is a blood-influx phenomenon; in a falling phase, there may be an aqueous-influx phenomenon in the same vein and the direction of flow may vary from hour to hour. If the determination of blood influx in glaucoma is ascribed to a difficulty experienced by the aqueous in escaping owing to organic narrowing and sclerosis of the outlets of Schlemm's canal, it is difficult to imagine how variations can occur so rapidly throughout the day; some other explanation must be sought.

What is an alternative explanation? It is

obvious that if a recipient vessel is compressed and the onward flow dammed back, the alternative of the filling of the vessels with blood or aqueous will be determined by the relative heights of the pressure in the aqueous vein and in the associated blood vein; for the contents of the vessel having the higher pressure will be pushed into the vessel with the lower pressure. This in turn will be determined by the height of the pressure in Schlemm's canal in the first case and the most proximal venous branching in the second—presumably often a branching near the venous exit from the eye.

If the aqueous pressure is higher than the venous pressure at this point, aqueous will fill up the afferent blood vein, that is, an aqueous-influx phenomenon will result. If, on the other hand, the venous exit pressure is the higher, the aqueous vein will fill up with blood and a blood influx will result. I think it is probably the locus of the first venous branching in the venous pressure gradient which determines whether any particular vein shows an aqueous or blood influx in the normal eye.

There is ample opportunity for very great pressure differences in venous pressure, for I have shown that just inside the sclera the venous pressure is slightly higher than the intraocular, while just outside the sclera it is almost the level of atmospheric pressure. There is thus a steep gradient of some 20 mm. Hg over a very short distance, and a slight difference in topography in the branching will be sufficient to cause great differences in the venous pressure at the proximal branching.

If this branching is just within the eye, the venous pressure here will be higher than the intraocular pressure, that is, higher than the pressure in the canal of Schlemm, and a blood-influx phenomenon will result. If the branching is just outside the sclera, the venous pressure will be less than the intraocular and an aqueous influx will result. Since the pressure relationships are always constant, or practically so, in the normal eye, the direction of flow for any particular vein is normally constant.

We have seen, however, that in glaucomatous eyes there is considerable circulatory instability which affects particularly the venous outflow pressure: if this varies, the influx phenomenon may also vary. In the rising phase of pressure (which usually occurs in the morning) we have seen that the evidence points to a high venous pressure: in the rising phase we therefore get a venous-influx phenomenon. In the falling phase, on the other hand, the evidence is that the venous pressure is low, and consequently we may get an aqueous-influx phenomenon in the same vein.

Although, because of this variation, we have concluded that an essential element in the determination of these phenomena cannot be structural and organic but must be circulatory and functional and that they are not entirely due to anatomic changes at or near the angle of the anterior chamber, there is no doubt that changes do occur at the angle. But I would suggest that they are adjuvant and not fundamental. If the safety-valve at the angle is acting freely, the effects of the vascular instability are compensated by drainage and rises of tension are controlled; if it is not, temporary or permanent rises in the ocular tension result.

It may be interesting to inquire at this stage if these structural changes, and also the changes in the optic nerve, can be associated with the underlying vascular inefficiency. It could quite well be that the block to the exit of fluid, so subtle in primary simple glaucoma as to be gonioscopically invisible, is due to a sclerosis around the exit channels or the trabecular tissue at the angle (which has been histologically verified), itself probably dependent upon a primary vascular sclerosis. Moreover, the pathologic picture of a cupped disc is typical of that commonly seen in any highly differentiated organ when the blood supply is gradually cut off—the more highly differentiated elements (in this case the nerve fibers) degenerate and

disappear and, owing to the lack of blood supply, there is no attempt at proliferation of the supporting tissues which themselves weaken and eventually degenerate. A very similar picture is seen in lacunar atrophy of the brain wherein the cerebral cortex degenerates in the same way in conditions of senile vascular sclerosis.

So far as the optic nerve is concerned in chronic simple glaucoma it is possible that an obliteration of the small vessels could be inaugurated by tension alone if it were sufficiently high and prolonged, but that this need not necessarily result is seen in the existence of tension in the absence of sclerosis (as in cases of hypertensive iridocyclitis) without the appearance of excavation of the disc. It is equally possible that a cupped disc might follow a vascular inefficiency or sclerosis in the absence of a pathologic tension and I think this does not infrequently occur in cases of glaucoma without tension. But it is certain that this appearance of the disc will occur most readily as a result of both tension and sclerosis acting together.

I, therefore, conceive primary simple glaucoma to be a condition characterized essentially by instability of vascular control and an impairment of the capillary endothelium and sclerosis, associated with instability of tension. If this is followed by sclerotic effects in the tissues affecting the whole eye, we get the typical picture of glaucoma simplex with raised tension; if it affects the posterior segment preferentially we get visual symptoms and excavation of the disc without tension; and if it affects the anterior segment, permanently raised tension is an early feature and the changes in the optic nerve are late.

It is true that, within the knowledge at our disposal, our methods of therapeusis are largely limited to the relief of the complication of tension. With miotic treatment, I think, we attack the disease more fundamentally, for drugs such as pilocarpine and eserine act, not merely by causing miosis, but by improving the circulation by dilating the capillaries and opening out new capillary districts, increasing blood-flow, and lowering the venous pressure. With surgical treatment we merely provide a mechanical relief for the complication of raised tension and leave the primary vascular process unaffected. And that, I think, is why the prognosis of so many cases of simple glaucoma is on the whole not good.

It is my impression that if the disease were not characteristic of age and our patients had a longer expectation of life, these figures would be worse. If the whole of the etiology of glaucoma were concerned with a raised tension and the whole of its treatment depended on the mechanical reëstablishment of drainage channels, the story of failures in the hands of enthusiastic surgeons would be very different.

That is not to say, of course, that the control of tension by operative treatment at as early a stage as possible is useless. Within the limits of our present konwledge, it is the only thing we can do; and if the raised tension is allowed to remain and progress, most of those eyes would go blind. The poverty of our results is merely a natural result of our confining ourselves to relieving a symptom—albeit an important symptom—and leaving the primary disease untouched.

To its amelioration—or better, to its prophylaxis—all our energies should be devoted.

The primary fault of all types of glaucoma is probably essentially vascular, whether the malady manifests itself in its congestive or simple form. To a certain extent the two types seem to be the opposites of each other producing the same effect—a failure of the circulation—the first an embarrassment by blood stasis, the second an inefficiency of blood supply.

To conceive glaucoma in terms of the drainage of the aqueous only, as is the habit among so many of us today, is to base our therapeusis on the evidence of the gross pathology which disease has left behind it, rather than on the more subtle initial changes depending on the underlying disordered physiology. It is as if we were to assess the

contributions of Rome to civilization by a study of the obscenities excavated at Pompei.

So, as we specialize more and more within the specialties of surgery, we are apt to forget that disease is rarely local; we are apt to lose sight of the whole in the consideration of its parts. The derangement of mechanics which appears as an end-result is so much more obvious than the initial failure in function: a rearrangement of mechanics is easy and since it gives relief, by all means let us practise it; but whatever we may say to our patients, do not let us say to ourselves that in this rearrangement we have solved the underlying problem or cured the disease. It is only when we get to understand the physiologic principles involved and trace these first subtle aberrations from normal that the relief we are able to give will have any likelihood of being complete, universal and permanent.

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GUMMAS OF THE EYELID

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Gummas of the eyelid were described in earlier textbooks and ophthalmic literature as being not too unusual. During recent years, only a few such case reports have appeared and practically all of these in foreign medical journals. Tertiary luetic lesions are becoming so infrequent that we rarely think of syphilis of the eyelid. The similarity of gumma to chalazion and the rareness of tertiary syphilis of the eyelids may, as it did in this case, cause the diagnosis to be missed.

De Schweinitz[1] says that, during the third stage of syphilis, occasionally ulcers and gummas appear in the lids, the latter often presenting a striking similarity to chalazions. These sometimes develop rapidly and undergo extensive ulcerative changes, producing ectropion, lagophthalmos, and so forth.

Fuchs[2] says gummas form indolent tumors which usually develop at the same time as gummas in other parts of the body. They resemble chalazion or hordeolum, but are distinguished by the fact that they break down into indurated painless ulcers, which have a lardaceous coating and tend to spread to the deeper parts, in some cases even perforating the lid.

Axenfeld[3] says that gummas of the eyelids are very rare, but they may be confused with hordeolum or chalazion. They must also be differentiated from tuberculosis. Syphilitic tarsitis is also deep-seated gumma; the skin process becomes more deep-seated and involves the tarsus.

Ball[4] says gumma is probably the most frequent of the syphilitic diseases of the eyelids. The lids become swollen and tense; ulceration follows. The ulcer has an irregular, eroded, punched-out appearance. Its floor is covered with dirty yellowish or gray debris and, if unchecked, there may be extensive destruction of tissues.

McKee[5] writes that gummas form indolent tumors which at the outset resemble chalazions or hordeolums but are distinguished from these in that they break down into indurated painless ulcers which tend to spread to the deeper parts, even perforating the tarsus. McKee reported the case of a man, aged 40 years, with an inflammatory ulcerative process involving the outer two thirds of the edge of the lower lid. There was rapid destruction of the tarsal plate with considerable loss of tissue. The Wassermann test was positive and the gumma cleared rapidly with antiluetic treatment.

M. Khali[6] described a nodular type of syphilitic tarsitis in which deep ulceration developed following circumscribed thickening of the tarsus. Gummas, unlike chalazions

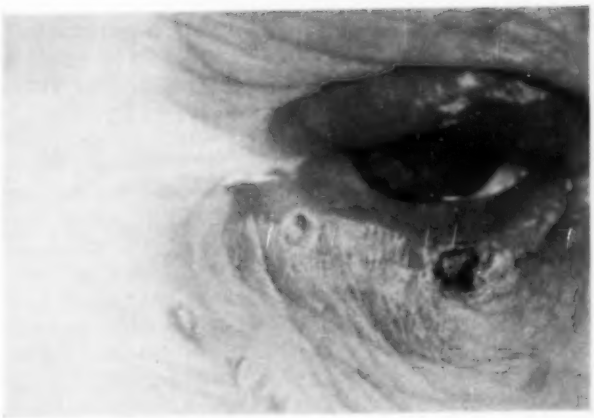

FIG. 1 (CASSADY). KODACHROME ILLUSTRATION OF THE GUMMATOUS INDURATION OF THE EYELIDS, WITH ECTROPION AND ULCERATION OF THE LOWER LID, BLEPHARITIS, AND SPARSENESS OF THE LASHES.

which they resemble, usually progress toward the skin and leave the conjunctival surface normal.

Ryss-Zalkind[7] reported an instance of gumma of the lower lid in a 21-year-old patient. The swelling was hard and indurated, finally reaching walnut size before it ulcerated. It subsided with only a small scar on antiluetic treatment.

Rifat Gozberk[8] described two very extensive ulcerations of the eyelids, which involved surrounding tissue of the malar bone, due to hereditary syphilis. The involvement of the lids was associated in each instance with other luetic, gummalike lesions. He emphasizes the differentiation of such lesions from lupus and malignancy.

Renard, Halborn, and Proux[9] described a gumma of the upper and lower eyelid in a 39-year-old woman. Both lids were red and edematous, adhered by thick conjunctival secretion, and covered by crusts. The external portion of the upper lid had an ulcer which extended to the palpebral edge. The lower lid was also ulcerated in its outer half exposing the tarsal conjunctiva. It was associated with bilateral optic atrophy. Serology was strongly positive for syphilis.

Renard and Halborn,[10] in a second article describing the palpebral manifestations of syphilis, present the same case and state that syphilis of the eyelids is usually seen in its tertiary stage, gumma or ulcerations. They believe that gumma of the lid is rarely encountered in its typical aspect because it evolves rapidly toward ulceration. At first the gumma resembles a chalazion. It is usually red and ulcerated on the skin side. Infiltration often involves the tarsus. The ulceration of a gumma is persistent, unlike that of a chalazion; it runs a chronic course. The serologic reaction is diagnostic. They also describe in detail three forms of syphilitic tarsitis—infiltrated, nodular, and marginal—which will not be discussed in this bibliography.

Genet[11] described a chalazionlike growth of the eyelid in a teen-aged girl that later proved to be a gumma of hereditary syphilis. A swollen indurated upper lid was associated with ulceration at the ciliary edge on the conjunctival surface of the tarsus. This was opened and the pulp of the ulceration curetted, but the inflammation did not regress in spite of the operation. The Wassermann test was found to be positive, and the lesion subsided with antiluetic treatment. Interstitial keratitis occurred in the same eye after treatment was started and later in the other eye.

Bujadoux[12] reported a gumma of the eyelid in a 55-year-old man that resembled a stye. A curetted biopsy of the palpebral tumor showed the microscopic appearance of a gumma. The eyelid lesion was associated with a painful corneal involvement. The lesion subsided with antiluetic treatment but no mention of the serologic reaction was found in the article.

Cornet,[13] in an article on various syphilitic eye manifestations, described syphilitic tarsitis as a sheet infiltration of the whole thickness of the eyelid. He pointed out its similarity to trachoma and its occasional association with conjunctival manifestations of trachoma.

Nazarov[14] described a gumma of the upper eyelid in a 57-year-old Russian woman. The tumor extended upward from the middle of the tarsus to the orbital rim. There was a ptosis of the lid, a narrowed palpebral fissure, and the eyeball was pressed downward by the tumor of the lid. The appearance of the skin was that of cyanosis; the tumor was hard and solid. The Wassermann test was positive and the tumor disappeared promptly with antiluetic treatment.

Lipovskaya[15] presented three cases of gumma of the eyelid from his clinic, more I believe than anyone else has found recently. The first case, a 47-year-old man, had a gumma of the upper lid which involved the tarsus and ulcerated through the palpebral conjunctiva. The Wassermann reaction was four plus. There was an associated gumma of the skin on the right shoulder.

The second case, that of a woman, aged 37 years, had a gumma which resembled a stye on her lower lid. It was of firm consistency. It ulcerated through and later a new induration close to it ulcerated. The eyelashes were destroyed. The ulcer had a deep yellowish appearance. The serology was strongly positive for syphilis. The ulcers healed with antiluetic treatment.

The third case, that of a woman, aged 34 years, was not strictly one of eyelid gumma but one of gumma which involved the lid from extension downward from a lesion on her eyebrow. The ulcer of the eyebrow was 3 by 1.5 cm. and was covered by a compact eschar. In the skin of the upper lid were scattered tiny ulcers, not coalescing. The diagnosis after a four-plus positive Sachs-Wibetsky test was serpiginous ulcerotuberculous syphilis. Deep keratitis of the eye accompanied the lesion.

Postic,[16] in 1940, comments upon the rareness of reports of gumma of the eyelids. He cited a case reported by Elschnig in which a contact gumma of the upper lid followed the appearance of a gumma below it in the lower lid. Ulceration of both lids occurred. Elschnig's explanation of the contact gumma was that of an allergic reaction which occurred in accordance with Noguchi and Klausner's conception of allergization of the skin to Spirochaeta and spirochetal products in luetics. Postic pointed out that we rarely have histologic findings from specimen excisions of the lids, such excisions being avoided because of the danger of deformity.

Postic's case was that of a 45-year-old woman who had noticed a small, well-circumscribed nodule in the inner third of her upper lid, It slowly enlarged and then a similar nodule appeared below it in the inner angle of the eye. Both of these nodules ulcerated and oozed pus. They were completely painless and her only complaint was the deformity. The lids were swollen, reddened, and ptosed. The ulceration of the upper lid was shallow with a grayish red surface and was about 3.5 mm. wide, with edema and induration around it. The ulcer of the lower lid was more extensively developed with a livid reddening of the skin. The Wassermann reaction was strongly positive.

A biopsy was taken from the lower and upper lid ulcers. The ulceration grew smaller with surprising rapidity and epithelization took place within a short time after institution of antiluetic treatment. The ulcers had rigid edges, hardening of their floors, and were unassociated with lymph-gland swelling.

The histologic specimens showed thickening of the epithelium, below which were extensive beds of large light epithelioid cells with giant cells of the Langhans type scattered among them. Within the epithelioid-cell aggregation there were sometimes numerous, rather large blood vessels with thin walls which invaded these aggregations of cells. These epithelioid cells showed only partial arrangement in nodules and were otherwise arranged in a more diffuse manner. Chronic inflammatory infiltration of the tissue occurred in the region of and between the epithelioid cells in connection with which lymphocytic elements and generous quantities of plasma cells were determinable.

Fundamentally the changes in this case were predominantly those of inflammatory granuloma, which could be either those of tertiary lues or of tuberculosis. The peculiar arrangement of the epithelioid cells and their invasion by numerous vessels would be an indication of lues rather than tuberculosis. The author was of the opinion that this case should be classed among the tuberous syphilides of the skin of the eyelid.

Postic[17] reported a second similar case with two opposing gummas of the medial third of the eyelids in a 29-year-old man. The lower lid had a small gray ulcer near the palpebral edge of the swollen lid. The opposing site of the upper lid presented macerated whitish-gray skin induration and impression ulcer. The Wassermann reaction was positive. The author emphasizes the contact nature of the gumma and points out that the

ideas of Noguchi and Klausner of the development of such contact gumma as a result of allergization of the skin to spirochetal products explain its origin.

Matteucci[19] described a serpiginous nodular syphilitic lesion of the lower lid of a 43-year-old woman which was so destructive as completely to destroy this lid. It started at the outer canthus of the lower lid and extended upward and backward over the entire left temporal region, then downward to about 2 cm. from the rim of the upper lid. It is not, I believe, a true gumma of the lid, although it was luetic. It probably, because of its nature and extent, should not be considered purely as a gumma of the eyelid.

Case report

History. I. C., aged 75 years, a farmer and widower, consulted me on March 8, 1946, because of swelling and ulceration of the lids of his left eye.

A nodule had appeared in his upper eyelid eight months previously, followed shortly by a similar one in the lower lid. Its early appearance was that of blepharitis associated with multiple chalazion, and it had been treated as such by another ophthalmologist.

Examination showed an ectropion of the left lower eyelid with a swollen, red upper lid. The vision was: O.D., 20/25; O.S., 20/30. The right eye appeared normal. The left upper lid was puffy in its entire length from the palpebral edge up to the lid fold. Besides the ectropion of the lower lid, there were several indurated skin ulcers on it, one central and one in the middle near its palpebral border. The central ulcer was covered with a dry black crust. There were several smaller ulcers farther down on the eyelid near the orbital rim. There were very few remaining eyelashes in either eyelid and these were covered with dry scales. The appearance was that of blepharitis with indurated ulcers of the upper lid and with ectropion and ulceration of the lower eyelid.

Except for a dry-crusted, indurated ulcer on the back of the neck, the remaining physical examination was not significant. This ulcer, 5 mm. in size, slightly larger than the one in the center of the lower lid, was also covered with a grayish black crust and was hard and infiltrated.

A biopsy specimen of the skin ulcer of the neck was taken and the specimen reported by Dr. Alfred Giordano of The South Bend Medical Foundation as follows: "The epidermis shows no significant hyperplasia. The underlying corium is the site of granulomatous tissue formation, there being numerous epithelioid cells which are not arranged in any significant pattern. These formations seem to surround the hair follicles and sweat glands. Numerous acid-fast stains revealed no organisms and no yeastlike organisms suggestive of blastomyces are seen. There is some mild thickening of the arterioles. Process could be a gumma but this cannot be proved. Pathologic diagnosis: Granuloma, etiology unknown."

The microscopic slides were also sent to Dr. E. T. Bell, department of pathology, University of Minnesota Medical School, and he concurred in the opinion that the lesion could be and probably was a gumma, at least its appearance was compatible with the diagnosis of syphilis.

The Mazzini flocculation test was three plus. The Mantoux test was mildly positive. During a two-week period, while the diagnosis was being established, the patient was given large doses of potassium iodide, which resulted in almost complete healing of the gummas. He was then treated in a neighboring city by his family physician with intensive penicillin therapy together with local eye drops of penicillin. A dermatitis of the eyelids started from the eye drops but subsided when these were discontinued. Within three weeks the lids were fairly normal except for the ectropion. The ulcers were healed, the swelling and infiltrations had subsided, and the upper lid appeared practically normal.

On May 9, 1946, Gaillard sutures were put in to correct the ectropion of the lower lid. This was unsuccessful so on May 20th,

a Kuhnt-Syzmanowski operation was done to correct adequately the ectropion of the lower lid. Following this, the eyes had a normal appearance, were healed, and showed no scarring from the ulceration.

Summary

A review of the literature with a bibliography of reported cases of gumma of the eyelid shows that it is an uncommon disease.

A report of a case with photograph is presented showing the resemblance of gumma to chalazion and induration of the eyelids.

Tertiary syphilis of the eyelids should be thought of if chalazions fail to heal, ulcerate onto the skin side of the lid, and are associated with other gummas.

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RETINAL DYSPLASIA*

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There are a number of conditions in infants and young children which produce a white reflex in the pupillary area as a result of opaque tissue back of the lens. These conditions are usually referred to collectively as pseudoglioma or pseudoretinoblastoma, but it seems illogical to apply these terms to the entire group merely because retinoblastoma must be considered in the differential diagnosis of some cases; for example, the question of melanoma must sometimes be considered in cases of detachment of the retina, but retinal detachments as a group should not therefore be called "pseudomelanoma." It is convenient, however, to have some designating term for this group of conditions in infants and children, and for this purpose we prefer "leukokoria," which suggests the one factor common to all cases; that is, the "white pupil." This term refers, of course, only to lesions back of the lens and therefore does not include congenital cataract.

Until a few years ago leukokoria was rare, and the isolated cases reported in the literature were described in such a variety of terms that it was impossible to deduce the existence of any very clear-cut clinical entities. In the past 10 or 15 years, however there has been a tremendous increase in the incidence of leukokoria and in the amount of attention directed to it. Terry was the first to appreciate this increase in incidence and gave illuminating reports of a condition which he called "retrolental fibroplasia." A great deal of speculation ensued as to the nature of this condition. It was not clear whether a new disease was involved or an increase in the incidence of an old disease, or whether or not the condition belonged to or was related to the cases of "remains of the hyaloid system" and "tunica vasculosa lentis." At first Terry thought it was so related. Reese and Payne felt that retrolental fibroplasia and remains of the tunica vasculosa lentis both represented persistence and hyperplasia of the primary vitreous but with different clinical manifestations and perhaps different etiologies. Krause thought that retrolental fibroplasia was essentially a retinal dysplasia and was associated with a cerebral dysplasia. It was the opinion of Owens and Owens that retrolental fibroplasia was essentially an acquired retinal angiomatosis and that it bore no relationship to the earlier sporadic cases of leukokoria.

Some order seems gradually to be emerging from this confused picture, and it is our belief that in congenital leukokoria three entities can now be recognized. These are of course not to be confused with leukokoria associated with such acquired lesions as metastatic retinitis, massive retinal fibrosis, and no doubt others not appreciated at the present time.

The three congenital manifestations of leukokoria may be identified briefly as follows:

1. *Retrolental fibroplasia* occurs primarily in premature infants and is the lesion which has shown the tremendous increase in incidence during the past decade or more.

2. *Persistent hyperplastic primary vitreous* occurs in full-term infants, is unilateral, and includes the cases referred to as "remains of the tunica vasculosa lentis." Its incidence has not increased.

3. *Retinal dysplasia,* which is to be described at some length in the present paper, occurs in the newborn and is not related to prematurity. It is always bilateral and the eyes are usually microphthalmic. Histologically the retina shows signs of dysplasia, usually with the formation of rosettes. The connective tissue behind the lens seems to be the persistent primary vitreous. The sec-

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ondary vitreous is usually deficient or not formed at all. In addition to the ocular changes, the affected infants show malformations elsewhere over the body. There are usually anomalies of the brain, heart, vascular system, or skeleton, one or another of which often causes an early death.

The simultaneous occurrence of malformations of the eye and brain early attracted the attention of ophthalmologists. It was the opinion of the early authors that in these cases the malformations of the brain were the cause of the ocular anomalies (Kundrat, Raehlmann). Later authors assumed that this combination was more of a coördination than a subordination (Ginsberg, Wehrli). Experimentally, malformations, and especially rosettes, can be produced in both organs by irradiation of the embryo with X rays (Yamagiwa).

The combination of malformations of the eye with anomalies of other organs than the brain seems to occur less frequently but is not rare. Malformations of the fingers and toes are not only a part of the Laurence-Moon-Biedl syndrome but can also be found in combination with other malformations of the eye. Ciotola has collected 15 such reports and added two of his own cases. A combination of eye and foot abnormalities is also characteristic of the Little and Bagg mouse tribe.

Survey of literature

Only a few cases have been reported in which retinal dysplasia with rosette formation has been found in combination with persistence of a retrolental embryonic tissue and with malformations of the brain or other organs. A review of the literature has revealed 15 cases, however, which we believe to be classifiable as retinal dysplasia, according to our definition.

1. Bernheimer published a report of the eyes of a baby whose full autopsy had previously been reported by Virchow. The child had hydrophthalmos and multiple malformations of the skeleton. Both eyes were microphthalmic, the retinas were detached and malformed, and no secondary vitreous was visible.

2. Doetsch described the eyes of a newborn baby. Both eyes were microphthalmic, the retinas showed many rosettes, and the mesodermal vitreous was hypertrophic, occupying the area behind each lens. The child had other malformations, such as cleft palate and lip.

3. Pichler described a similar case in his monograph on the pathologic anatomy and pathogenesis of bilateral microphthalmos. This baby also had cleft palate and lip. The retina was detached and showed rosette formation.

4. Monthus and Opin reported the autopsy of a newborn infant that had polydactyly, cleft palate and lip, and no cerebral occipital lobes. Both eyes were small, the retinas showed rosette formation, and only the vascular vitreous was present. The shrinking of the vascular vitreous had led to a complete detachment of the retina.

5. In the case reported by von Hippel the retinas in both eyes showed rosette formation and were completely detached, forming a sagittal septum behind the lens. This newborn baby also had polydactyly, cleft palate and lip, and a congenital defect in the skull.

6. In the case reported by Lafon the eyes showed the same picture with detached retina and rosettes, persistence of primary vitreous, and microphthalmos. Unfortunately, no general examination of the newborn was reported.

7. The second infant reported by Rochon-Duvigneaud and Coutela showed a bilateral retinal detachment with rosette formation and embryonic connective tissue behind each lens. The baby had hydrocephalus and died when 16 months of age. Although there were no inflammatory signs in either eye, the authors, following the trend of their time, assumed an inflammatory genesis of the condition.

8. In Fleischer's case, a newborn with polydactyly, syndactyly, cleft palate, and hare lip, a similar condition was found in both microphthalmic eyes. In addition to the changes of the retina and of the connective tissue behind the lens, there was a coloboma of the eye. Fleischer emphasized the importance of a persisting adherence of the mesodermal parts of the primary vitreous to the inner layer of the secondary optic vesicle.

9. Yudkin reported a case in which multiple congenital anomalies of the body (fingers, heart, diaphragm) were combined with malformations in both eyes of a newborn baby. The retinas in both microphthalmic eyes were folded and showed rosette formation. A fibrovascular mesoblastic tissue covered the area behind each lens.

10. Similar malformations of the eye were reported by Harris and Thomson in a newborn that showed, in addition, multiple congenital defects of the vascular system, polydactyly, and an orbital cyst.

11-15. Krause dealt recently with leukokoria in an excellent article. On the basis of simultaneous

brain changes he called the disease "congenital encephalo-ophthalmic dysplasia," and added 18 of his own cases. It has been our observation of this condition, however, that simultaneous malformations of other parts of the body are at least as frequent as congenital defects of the brain and that there is therefore no reason to call it "encephalo-ophthalmic" dysplasia. On the other hand, it is the dysplasia of the retina that characterizes the ocular changes in these cases and has moved us to propose the term "retinal dysplasia." In any event, only five of Krause's cases (Nos. 6, 8, 9, 10, and 14) seem to us to belong to this group. Four of the five had hydrocephalus and severe changes of the brain, and one (No. 10) had microcephaly and cerebral agenesis. The retinas of these cases showed severe malformations with gliosis, and, in one case, rosettes. These five were the only cases in the series that could be regarded as full-term babies and that were classified as such by Krause. In three of them (Nos. 8, 9, 10) delivery was at term. The other two were delivered after what was supposed to be a shorter time of gestation but the birth weights were 2,840 and 3,410 gm., respectively.

Krause's remaining 13 cases were premature babies with the typical lesions of retrolental fibroplasia. They had no cerebral symptoms other than mental retardation, spasms in one case (No. 12), and spastic quadriplegia in another (No. 16). The diagnosis of mental retardation in these blind, premature children is necessarily open to doubt and probably does not warrant postulating a cerebral malformation. On the basis of a clinical ophthalmic examination alone, and without sufficient evidence of a cerebral lesion or other malformation, the diagnosis of retinal dysplasia cannot be made with certainty. These 13 cases would thus seem more properly to be classifiable as cases of retrolental fibroplasia.

Walker reported a case of lissencephaly with ocular changes somewhat resembling those of the entity under discussion, but the clinical picture was not that of a typical leukokoria. This was equally true of Wehrli's case in which hypoplasia of the retina was coördinated with a macrogyria and microgyria of the brain. In our opinion, therefore, these two cases should not be classified as "retinal dysplasia."

Report of cases

Case 1

Baby H (540,674). The baby was born prematurely according to the calculated period of gestation, but the birth weight was 2,770 gm. The infant was poorly developed and displayed syndactylism, polydactylism, and cleft palate. Oxygen was administered but the child died 55 hours after birth.

Autopsy (Sloane Hospital No. 2,573)

Congenital abnormalities of the heart (atrophy and stenosis of pulmonary artery, hypertrophy of ductus arteriosus, partial defect of ventricular septum, right transposition of the aorta, congenital dilatation and hypertrophy of the right side of heart), congenital absence of right hypogastric artery, polydactylism of right hand and both feet, congenital fracture of right parietal bone, papilloma of tongue, accessory lobe of spleen and liver, partial cleft palate. The brain was not examined histologically.

Histologic examination of the eyes (Pathology No. 1,287)

O.D.: The eye was of normal size. The cornea was normal. There was a coloboma of the iris. Remnants of the pupillary membrane stretched from one collarette to the other, some of them adherent to the posterior surface of the cornea. The angle of the anterior chamber was of fetal character. The ciliary body, choroid, and sclera were normal. The retina was partly detached, forming small folds in the posterior part. There were several hemorrhages in the superficial retinal layers and a more extensive hemorrhage near the ora serrata where it produced a retinal detachment. The pigment epithelium and rudimentary retina, forming a fold, covered the ciliary body and, stretching over to the lens, covered most of its posterior surface together with the membrana vasculosa lentis. The hyaloid artery could be traced from the disc to the posterior surface of the lens where it branched out to form the vascular membrane. The lens showed cataractous changes in the posterior cortex and near the anterior pole. The lens epithelium extended nearly to the posterior pole.

O.S. (fig. 1): The eye was smaller than normal. The cornea was normal. The iris was complete. Remnants of the pupillary membrane were present. The angle of the anterior chamber was of fetal character. The ciliary processes were partly missing. The retina was completely detached. The mass of the retina lay behind the lens, forming many folds. The formation of true rosettes was very conspicuous. There was hyaline degeneration and some calcification in the retina. The retina was firmly adherent to a dense vascularized sheath of connective tissue that covered the posterior surface of the lens. The hyaloid artery could be seen in the stalk of the detached retina. The lens was dislocated posteriorly and showed cataractous changes in its cortex. The pigment epithelium showed some proliferation.

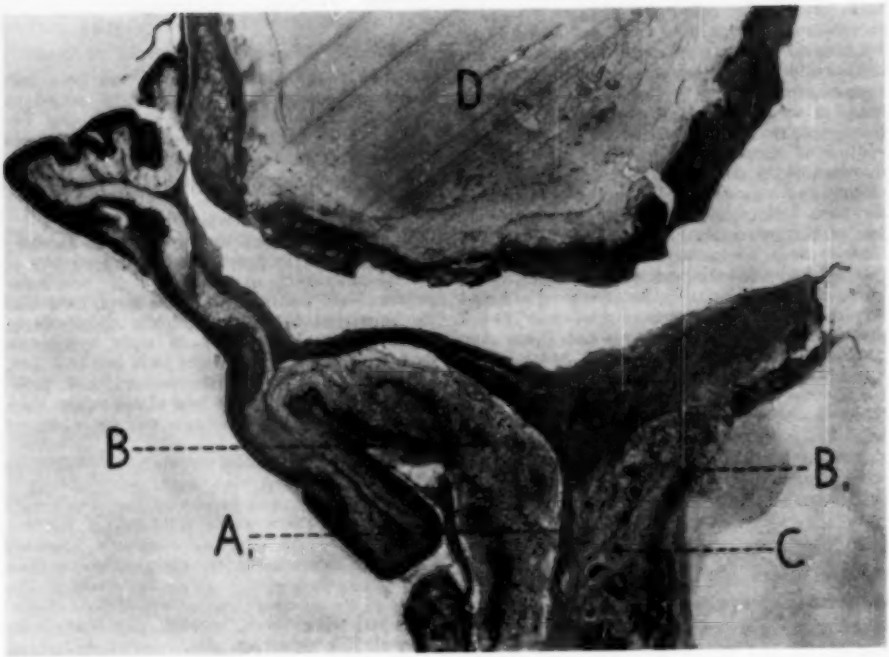

Fig. 1 (Reese and Blodi). Section of the eye of Case 1 obtained at autopsy. The persistent primary vitreous (A) extends down (A_1) into the funnel of the detached retina (B-B_1), which contains true rosettes (C). The separation of the lens (D) from the retrolental tissue is an artefact. No secondary vitreous has formed.

CASE 2

C. B. (548,408). The baby was born at term and developed normally, except for his vision, up to two years. No eye diseases or malformations were known to exist in the family. Soon after delivery the father noticed a white shadow in both eyes and took the child to the Institute of Ophthalmology for examination.

Ophthalmic examination (under ether anesthesia)

O.D.: Cornea steamy; anterior chamber, iris, and lens probably normal. There appeared to be a gray mass in the vitreous chamber with its anterior surface concave and near the posterior capsule of the lens. No hemorrhages could be seen, but parts of a few newly-formed vessels were visible on the gray surface. Transillumination: No interference. Tension: 73 mm. Hg (Schiøtz).

O.S.: Cornea clear; iris and lens apparently in good condition. The appearance behind the lens was much like that of the other eye, but what seemed to be a gray membranelike structure was farther back than it was in the right eye and was not complete. Apparently there was some vision in this eye. Tension: 22 mm. Hg (Schiøtz). Transillumination: No interference.

The right eye was enucleated when the baby was seven weeks old. At three years of age a follow-up examination revealed the following:

O.S.: There was almost no anterior chamber and the pupil was small and occluded by a white tissue which also was seen along the surface of the iris, especially over the upper portion. The iris was bound down by synechias. Tension: 35 mm. Hg (Schiøtz). The examination under general anesthesia also showed definite newly formed blood vessels in the iris with question of an iris bombé. The eye remained irritable and the child cried, apparently from pain. Pilocarpine did not help and a cyclodialysis was performed.

Because of increasing signs of mental retardation, the boy was admitted to the Neurological Institute of New York. He was subsequently removed to a state school because of mental deficiency and imbecility. He died in a state of cardiac collapse when seven years old. An autopsy was not performed.

Histologic examination of the right eye (Pathology No. 1,356) (fig. 2)

The cornea was normal. There was almost no anterior chamber. In the central part the lens was in contact with the posterior surface of the cornea. In addition there were a few broad anterior synechias of the iris. The angle of the anterior chamber was fetal in type. The uvea was normal. The retina was completely detached and firmly adherent to a mass of loose connective tissue that covered the posterior surface of the lens and extended into the cone of the detached retina. The tissue contained a few larger vessels, blood cysts, and hemosiderin. The retinal elements had largely disappeared but there were several islands of nuclear elements. In some instances the remaining retinal cells formed true rosettes. On the temporal side of the detached retina there was a large retinal cyst filled with a clear fluid. In the subretinal space there was a considerable amount of blood. The ciliary processes were adherent to the retrolental tissue and were pulled toward the lens. The posterior lens capsule was intact but wrinkled.

CASE 3

M. C. (730,048). This child was born at term by a precipitate delivery at home. There were no eye diseases or malformations known to exist in the family. An older sister was normal and well. The parents noticed a hare lip and brought the infant to the Babies Hospital. On examination a cleft palate, polydactylism, and heart murmurs were also found. On admission the weight was 2,335 gm.; the child was then 35 hours old.

Ophthalmic examination

The lids could be opened with great difficulty only, but glimpses of rudimentary globes could be obtained. The globes could be palpated through the lids and were estimated to be about 5 mm. in diameter. Diagnosis: Congenital microphthalmos.

When the child was 20 days old she was operated on for correction of her cleft palate and lip. She died the following day.

Autopsy (Babies Hospital No. 6,833)

Congenital malformation of the heart and tetralogy of Fallot with stenosis of the pulmonary conus, cleft palate and hare lip, polydactylism of both hands, polycystic kidneys, uterus bicornis, cystic fibrosis of pancreas, diaphragmatic hernia, atelectasis and interstitial pneumonia, acute splenic tumor. Gross examination of the brain did not reveal any abnormality except that the leaflets of the septum pellucidum were found to be broad bands of cerebral tissue which were not joined in the midline except at their dorsal extremities. Microscopic examination of the cerebrum was not made.

Histologic examination of the eyes (Pathology No. 2,919)

O.D. (fig. 3): The eye was microphthalmic. The cornea was normal. There was a colobomatous defect of the iris and extensive posterior synechias

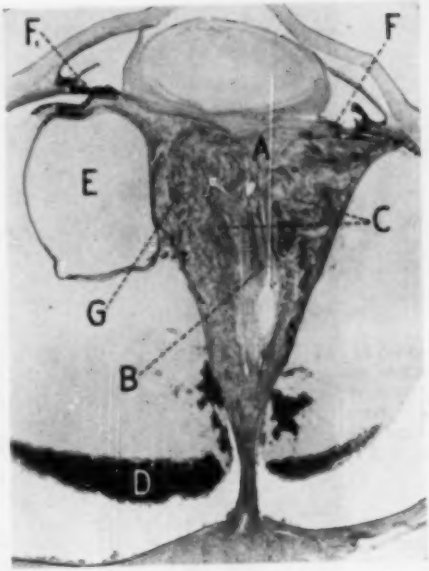

Fig. 2 (Reese and Blodi). A section of the eye of Case 2. The persistent primary vitreous at (A) extends down into the funnel (B) of the detached retina (C). (D) represents subretinal hemorrhage, and (E) a retinal cyst. Elongated processes (F) and (F_1) extend into the retrolental tissue. The retina is composed of undeveloped embryonic tissue with true rosettes at (G) and elsewhere. The secondary vitreous has failed to form.

were present. Remnants of the pupillary membrane covered the anterior surface of the lens. A cyst of the epithelial layers of the iris pushed the iris forward on one side. The ciliary processes were scarce. The bulk of the retina was detached and firmly adherent to a vascularized embryonic connective tissue behind the lens. The retina was composed of undeveloped embryonic tissue with numerous rosettes. The secondary vitreous had failed to form. The lens showed marked cataractous changes.

O.S.: This eye displayed similar malformations. There was in addition a small retrobulbar cyst, the wall of which was in connection with the sclera. There was also a coloboma of the choroid and of the optic nerve. The main bulk of the retina was detached and lay as a folded mass back of the lens, showing marked disintegration. The formation of rosettes was conspicuous. Only a small part of the inferior retina was in situ. The lens showed marked cataractous changes with extension of the epithelium around the posterior circumference. There was some proliferation of the pigment epithelium.

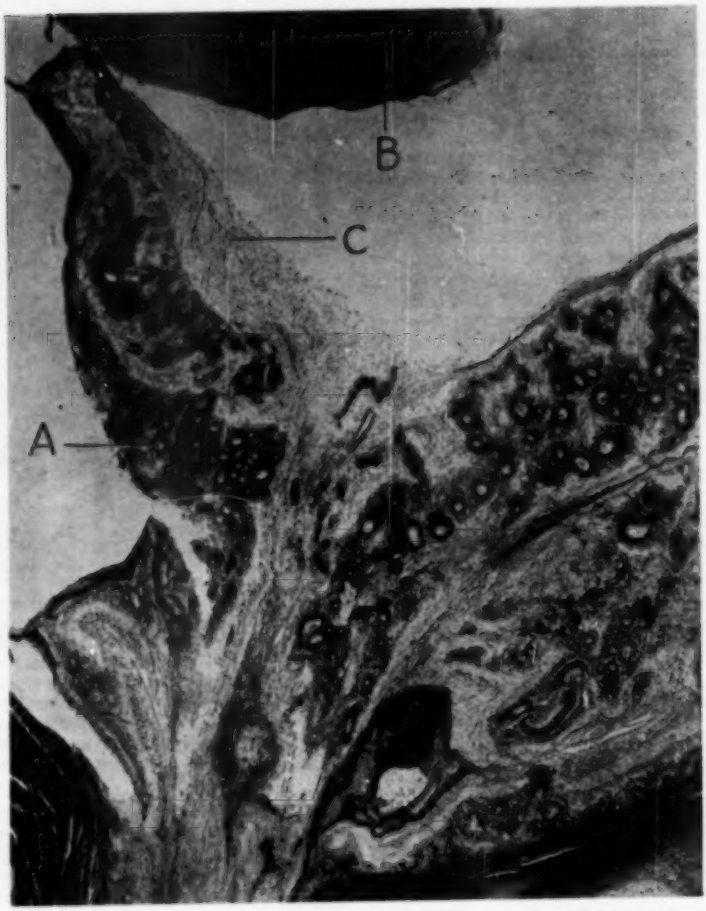

Fig. 3 (Reese and Blodi). Section of the eye of Case 3 with a completely malformed retina showing many rosettes at (A) and elsewhere. Behind the cataractous lens (B) is a vascularized embryonic tissue (C) representing the primary vitreous. No secondary vitreous has formed.

CASE 4

C. K. This baby was born two-and-one-half months before term. When she was three months old she was brought into a hospital in Virginia.

Ophthalmic examination (Dr. K. Kundert)

There was bilateral buphthalmos and the corneas were somewhat steamy. In both eyes there were retrolental membranes that appeared to be vascularized. The fundus could not be seen and the tension was elevated. X-ray studies of the orbits showed no calcification. Two months later the right eye failed to transilluminate and was enucleated. Four months later the left eye no longer transilluminated and was enucleated. Unfortunately we do not possess a slide or a report on the left eye. Seven months later the child died.

Autopsy (personal communication from Dr. K. Kundert)

Hydrocephalus of the right lateral and third ventricles with narrowing of the cerebral aqueduct.

Histologic examination of the right eye (Pathology No. 3,558)

The eye was larger than normal. There was a slight edema of the cornea. In the anterior chamber there was a pinkish fluid. The peripheral parts of the iris were plastered against the posterior surface

of the cornea. The ciliary body and the choroid was normal. The retina was totally detached and lay folded up behind the lens. The retinal elements were disintegrated and rosettes could be seen. In the stalk that connected the optic nerve and the retina behind the lens, a vessel lay centrally that could have represented a persistent hyaloid artery. The fibers of the optic nerve were pulled forward, giving the impression of a persistence of the primitive epithelial papilla of von Szily. At the posterior end of this stalk was a nodule of hyalinized tissue with some retinal elements. Behind the lens lay a loose connective tissue with several large vessels and two blood cysts. The detached retina was firmly adherent to that tissue. There was old blood in the subretinal fluid. The lens showed slight cataractous changes.

CASE 5

Baby K (862,502). This baby was born at term with a birth weight of 2,520 gm. Several malformations were noticed at birth. They included polydactyly, umbilical hernia, undescended testes, and bilateral microphthalmos. The condition of the child after birth was poor and he died 13 hours after delivery.

Autopsy (Sloane Hospital No. 3,472)

Malformations of the heart with patent foramen ovale and patent ductus arteriosus and of the vessels (absence of left innominate vein, persistent left superior vena cava, absence of left hypogastric artery), polydactylism, omphalocele with herniation of intestine, undescended testicles, malformation of frontal bone. Aspiration of amniotic fluid and meconium. Gross examination of the brain showed no pathologic changes. No microscopic examination of the cerebrum was made.

Histologic examination of the eyes (Pathology No. 3,909)

O.D. (fig. 4): The eye was smaller than normal. There was a coloboma of the iris and remnants of the pupillary membrane extended through the anterior chamber. The ciliary body and the choroid were normal. The peripheral part of the retina was artificially detached and well developed. Behind the lens in the central part there was a dense connective tissue with some large vessels. Peripheral to that tissue were smaller vessels on the posterior surface of the lens as remnants of its vascular sheath. The central part of the retina was firmly attached to that connective tissue and therefore completely detached, forming in this way a retinal fold. The retinal elements of this part were largely disintegrated and rosette formation was characteristic of the region. The nerve fibers of the optic nerve were pulled forward as in Case 4. There was a vessel in the central posterior part of the stem of the detached retina that could have represented a persistent hyaloid artery. The lens shows extensive cataractous changes with proliferation of the capsule, sometimes in the form of drusen, and with extension of the epithelium around the whole circumference.

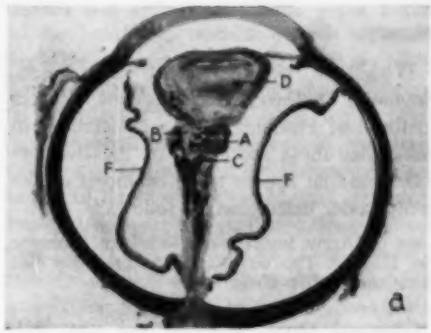

Fig. 4a (Reese and Blodi). The section of the eye of Case 5 showing the adherence of the central part of the retina (A) to a retrolental connective tissue (B) forming a fold with many rosettes at (C). The lens (D) is cataractous. The detachment of the peripheral part of the retina (F) is an artefact.

O.S.: This eye was approximately the same size as its fellow. The cornea was normal. The angle of the anterior chamber was of fetal character. Extensive remnants of the pupillary membrane crossed the anterior surface of the lens. There was a coloboma of the choroid. Only a small part of maldeveloped retina was in situ. The main part of the retina was detached and lay coiled up behind the lens. The retinal elements were largely disintegrated and calcium was deposited. Rosettes could be seen throughout this region. Behind the lens was a connective tissue with many large vessels. Elongated ciliary processes were adherent to the tissue which extended into the stalk of the detached retina posteriorly to the optic nerve. No

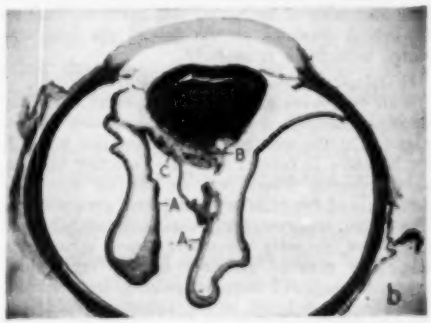

Fig. 4b (Reese and Blodi). A more peripheral section of the same eye as in Figure 4a. It shows the formation of a retinal fold (A-A_1) by the adherence of the central part of the retina (B) to the retrolental tissue (C).

hyaloid artery could be seen. The lens showed cataractous changes.

With the permission of Brig. Gen. Raymond O. Dart, director, Armed Forces Institute of Pathology, we are including in this series those specimens of the Institute collection that appear to be examples of the entity under discussion, as follows:

CASE 6 (Army Institute of Pathology Accession No. 132,027). This was a full-term baby that died three hours after birth.

Autopsy

Congenital cardiac anomalies and other malformations.

Histologic examination of the eyes

The retinas of both eyes were detached and folded and displayed many rosettes. On the posterior lens surface there was a dense fibrous tissue with which the retina was firmly connected.

CASE 7 (Army Institute of Pathology Accession No. 135,013). This baby died when seven days old.

Autopsy

Hare lip, cleft palate, clubbed hands and feet. The orbits, optic nerves, chiasm, and optic tracts were small.

Histologic examination of the eyes

Both eyes were microphthalmic. There was a coloboma of the iris. The retinas were detached and folded and showed true rosettes. Behind the lens was a vascular tissue which was densely attached to the detached retina. The lenses showed cataractous changes and the epithelium extended on the posterior surface.

CASE 8 (Army Institute of Pathology Accession No. 136,819). Contributed by Dr. C. L. Reed, Pittsburgh, Pennsylvania. This four-month-old baby was born at term and was evidently feebleminded. A bilateral growth behind the lens obscured both fundi from birth.

Histologic examination of the eyes

Both eyes were apparently of normal size. The anterior chamber was shallow, in some places missing. In the central part, the anterior pole of the lens was in contact with the posterior surface of the cornea. There was an anterior synechia. Remnants of the pupillary membrane were present. The retina was completely detached and adherent to a loose, vascular connective tissue behind the lens. The nervous elements of the retina had partly disintegrated but true rosettes were visible. There was old blood in the subretinal fluid.

DISCUSSION

Retinal dysplasia is a bilateral congenital malformation manifesting itself at birth in full-term infants in association with cerebral agenesis and congenital anomalies elsewhere over the body.

OPHTHALMIC FEATURES OF RETINAL DYSPLASIA

Clinical features. The eyes of babies with retinal dysplasia are usually smaller than normal eyes although there is considerable variation in the degree of microphthalmus. In one case in this series the eyes were so small that they could hardly be seen in the orbits. In other cases the smallness of the eyes was hardly appreciable, and in one (case 4) the eyes were buphthalmic as a sequela to secondary glaucoma.

Retinal dysplasia is always bilateral, and if the eyes can be examined clinically the findings are very much the same in all cases. There is dense opaque tissue behind the lens which obstructs any view of the interior of the eye. The lens may be clear in the beginning but usually becomes cataractous. A secondary glaucoma may follow, probably from malformation of the filtration angle. The anterior chamber is shallow and remnants of the pupillary membrane may be visible.

Pathologic features. The pathologic features of retinal dysplasia are characteristic and should provide sufficient criteria for accurate diagnosis. Both eyes are usually affected in the same degree. The most conspicuous feature is malformation of the retinal elements with the formation of true rosettes. The retina is detached in part or totally and lies in folds against, and enmeshed in, a vascularized connective tissue just back of the lens. This fibrous tissue is viewed as the persistence of some of the primary vitreous. The total or partial detachment of the retina therefore represents a union of the retina to a part or all of the primary vitreous, with a failure of the secondary virtreous to form over this area of coaptation. The dyplasia of the retina manifests itself, therefore, not only by the malformation of retinal elements and the formation of rosettes, but also by the lack of

formation of a secondary vitreous by the retina. The retinal malformation may be associated with other ocular anomalies such as coloboma of the uvea or optic nerve, or retrobulbar cyst.

Differential diagnosis

The clinical picture presented by other types of leukokoria may resemble that of retinal dysplasia to such an extent that clinical recognition of the syndrome must depend on the fact that it is bilateral, unrelated to prematurity, and associated with other abnormalities. Retrolental fibroplasia occurs characteristically in premature infants, is not associated with mental retardation or congenital malformations elsewhere, except skin hemangiomas, and usually presents a reasonably characteristic clinical picture which includes the presence of long ciliary processes around the periphery of the retrolental tissue. Persistent hyperplastic primary vitreous (tunica vasculosa lentis) is unilateral in full-term infants, is not associated with abnormalities, and usually has a distinctive clinical appearance, covering only the central part of the posterior surface of the lens.

Association with other malformations

Association of the eye lesions of retinal dysplasia with malformations of other parts of the body is characteristic. Many other organs can be affected, and, while anomalies of the brain are conspicuous, malformations of the heart and vascular system are more frequent, at least in our series, and are probably the cause of the early death of most of the affected babies.

Association with anomalies of the cerebrum was emphasized by Krause. In our series of eight cases, we found anatomic evidence of cerebral malformations in one case only (case 4). In two other cases (2 and 8) marked signs of feeblemindedness constituted the only evidence of a brain anomaly, but in spite of the fact that mental retardation alone does not, in our opinion, justify the diagnosis of retinal dysplasia, these cases were included in the series because of the typical pathologic features of the enucleated eyes. These three cases, in which we know of, or assume, a cerebral malformation, had no other malformations so far as we know, but it must be borne in mind that one of them (case 8) is alive and may have malformations of the internal organs which have not been diagnosed, that the autopsy report of the second (case 4) is incomplete, and that in the third (case 2) no autopsy was performed.

Association with malformations of the heart and vascular system occurred in five of our cases (1, 2, 3, 5, and 6). The anomalies varied from case to case but were severe enough in all instances to cause early death. In one case (2) in which there was no autopsy, the cardiac condition was assumed from the clinical picture shortly before death.

TABLE 1

Combination of retinal dysplasia with other malformations

Case	Heart	Vascular System	Brain	Polydactylism	Hare Lip Cleft palate
1	+	+			
2	+		Feeble-minded	+	+
3	+	+			
4			+	+	
5	+	+			
6	+				+
7					
8			Feeble-minded		

Polydactylism was associated with the ocular anomalies in three cases of our series (1, 3, and 5), and cleft palate and hare lip in three (1, 3, and 7).

The various combinations of these malformations as they occurred in our series are shown in Table 1.

Summary and Conclusions

1. The term "leukokoria" is applied to the group of conditions in infants and young children which produce a white reflex in the pupillary area as a result of opaque tissue behind the clear lens. It is suggested that the congenital forms of leukokoria may be differentiated as follows: (a) retrolental fibroplasia, (b) persistent hyperplastic primary vitreous, and (c) retinal dysplasia.

2. Retinal dysplasia is defined as a bilateral congenital malformation manifesting itself at birth in full-term infants in association with cerebral agenesis and congenital anomalies elsewhere over the body.

3. Fifteen cases reported in the literature belonging, in our opinion, to the group designated as retinal dysplasia are described briefly and eight additional cases studied by us are reported in detail.

4. The clinical and pathologic characteristics of retinal dysplasia, its differential diagnosis, and its association with congenital anomalies of other parts of the body are discussed.

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SOME EFFECTS OF INJECTION OF HYALURONIDASE INTO THE ANTERIOR CHAMBER*

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Hyaluronic acid is one of the mucopolysaccharides making up the intercellular ground substance of connective tissue. It tends to bind water in the interstitial spaces and holds cells together in a gelatinous medium. This gel is apparently an important factor in the transfer of water and metabolites in the tissues.

Meyer[1] has demonstrated hyaluronic acid in the aqueous and vitreous of the eye. Meyer and Chafee[2] have also isolated a monosulfuric acid ester of hyaluronic acid from the cornea which they called hyaluronosulfuric acid. This ester could not be found in the sclera and apparently is contained in the substantia propria of the cornea. They postulated that it was intimately concerned with the transparency of the cornea as well as the absence of blood vessels.

CHARACTERISTICS OF HYALURONIDASE

Hyaluronidase† is one of the so-called spreading factors and is probably an important component of all spreading factors of biologic origin. It is an enzyme which produces a depolymerization and then a hydrolysis of hyaluronic acid. In purified form it only depolymerizes. It has the same effect on chondroitin sulfate of hyaline cartilage and hyaluronosulfuric acid of the cornea. Meyer[3] has demonstrated that 95 percent of the hyaluronic acid present in the aqueous is in a depolymerized nonprecipitable form because of the presence of hyaluronidase in good concentration. Von Sallmann[4] has observed a more rapid absorption of erythrocytes from the vitreous of rabbits after injection of hyaluronidase into the vitreous.

It is possible that the concentration of hyaluronidase in the aqueous may have some relation to its filtration. Chain and Duthie[5] found that the spreading factor of testicular extract‡ reduced the viscosity of synovial fluid. This suggests the possible use of hyaluronidase to reduce the viscosity of the aqueous and thus promote flow. The secondary glaucoma that frequently complicates acute anterior uveitis is, in its early stages, no doubt largely caused by an increased viscosity of the aqueous. One can easily see the possible use of hyaluronidase in this type of secondary glaucoma.

The importance of the enzyme in primary glaucoma is more difficult to postulate. One must then consider the mucopolysaccharides contained in the angle of the anterior chamber.

EXPERIMENTAL AND CLINICAL STUDIES

Our studies were prompted by a desire to learn more about the importance of hyaluronidase in glaucoma.

Hyaluronidase was injected directly into the anterior chamber of 16 normal rabbits in order to determine the effect on the intraocular pressure of the normal eye. The fellow eye of each rabbit was injected with a 0.85-percent solution of sodium chloride as a control. Observation for a period of 72 hours failed to reveal any significant effect on the intraocular pressure of these rabbits.

At the same time that the rabbit experiments were being performed, two patients

* From the Department of Ophthalmology, University of Pittsburgh, School of Medicine, and the Eye and Ear Hospital. This work was aided by grants from the Addison H. Gibson Laboratory and the Ophthalmic Foundation of Pittsburgh. Presented at the eighteenth scientific meeting of the Association for Research in Ophthalmology, Philadelphia, June, 1949.

† The hyaluronidase used in these studies was furnished by Schering Corporation, Bloomfield, New Jersey.

‡ Testicular extract is one of the most potent sources of hyaluronidase.

were admitted to Eye and Ear Hospital for the treatment of acute nongranulomatous anterior uveitis with secondary glaucoma. The tension was not controlled in either case by the usual therapeutic measures. Since the situation appeared hopeless and loss of the involved eye imminent, it was decided to instill hyaluronidase into the anterior chamber of each patient.

CASE REPORTS

Case 1

History.—Mrs. M. B., aged 49 years, was first seen in the eye clinic, June 2, 1948, complaining of redness of the left eye of 10 days' duration and pain in the eye for the past three days. She had never had any previous eye disease.

Ocular examination. Vision of the right eye was 20/30 and of the left eye 20/50 with her present correction.

External examination of the left eye revealed mild edema of the lids, marked bulbar injection, and a cloudy cornea.

Biomicroscopy of the left eye revealed an edema of the corneal epithelium and stroma of mild degree, numerous fine keratic precipitates, and an aqueous flare. On dilation of the pupil, posterior synechias were observed at the 5- and 8-o'clock positions.

Ophthalmoscopy revealed the ocular media to be so cloudy that no fundus details could be seen. The intraocular pressure was 66 mm. Hg (Schiøtz).

No abnormality of the right eye was found.

Systemic survey. Physical examination revealed moderate obesity, mild arthritis, and swelling of the right ankle as the result of an old thrombophlebitis. Dental survey revealed severe marginal gingivitis with alveolar absorption, many apical abscesses, and very poor oral hygiene. Chest roentgenogram was negative. The urine and blood were normal.

Treatment. The patient was admitted to the Eye and Ear Hospital when first seen. A paracentesis of the anterior chamber was performed on admission. Atropine and hot compresses were prescribed locally. Foreign protein in the form of boiled milk was administered and the dental foci were removed. Penicillin was administered before and after dental surgery.

The original paracentesis was reopened daily for six days. In each 24-hour period, the tension would rise again to between 62 and 66 mm. Hg (Schiøtz). On the seventh day, after springing the paracentesis wound, the anterior chamber was irrigated with a freshly prepared solution of hyaluronidase (one turbidity reducing unit per cubic centimeter). On the following day, the tension had risen again to 49 mm. Hg (Schiøtz). Irrigation was again performed with hyaluronidase after allowing the aqueous to escape. The tension 24 hours after this second instillation of the enzyme was 36 mm. Hg (Schiøtz). A subsequent irrigation with the enzyme three days later failed to produce the same reduction of tension and no further irrigations were performed. The uveitis subsided a few days thereafter and the patient was discharged from the hospital 17 days after admission.

The tension remained around 35 mm. Hg (Schiøtz) for two more months before returning to normal and remaining there. At this time, retroillumination with the slitlamp revealed definite iris atrophy.

Case 2

History. Mrs. J. R., aged 37 years, was admitted to the Eye and Ear Hospital on June 5, 1948. She stated that her left eye had been inflamed eight months before but responded to treatment by her local eye physician. Two weeks prior to admission, she bumped her left eye following which it became red and painful.

Ocular examination. External examination of the left eye revealed moderate edema of the lids, marked bulbar injection with a deeply pigmented conjunctival nevus at the 9-o'clock position, and a cloudy cornea.

Biomicroscopy of the left eye revealed moderate corneal edema, a heavy deposit of fine keratic precipitates, aqueous flare, and many posterior synechias preventing adequate dilation of the pupil.

Ophthalmoscopy revealed a red reflex, but no fundus details could be seen because of the cloudy media. The intraocular pressure was 66 mm. Hg (Schiøtz).

No abnormality of the right eye was found.

Systemic survey. Physical examination was negative except for a blood pressure of 160 mm. Hg (systolic) and 100 mm. Hg (diastolic). Dental survey revealed complete decay of upper incisors with moderate alveolar absorption. Laboratory studies of blood and urine failed to reveal any etiologic factor.

Treatment. Atropine sulfate and hot compresses were used locally. Foreign-protein therapy in the form of boiled milk intramuscularly was administered on four occasions at four-day intervals. A good febrile response was obtained each time.

A paracentesis of the anterior chamber with a retrobulbar injection of 1.5 cc. of procaine hydrochloride was performed on admission. The paracentesis incision was reopened daily for four days but the tension rose to a high level after each of these openings. On the fifth day, the tension was 77 mm. Hg (Schiøtz).

Following the reopening of the corneal incision on this day, the anterior chamber was irrigated with a freshly prepared solution of hyaluronidase (one turbidity reducing unit per cubic centimeter). The tension was normal 24 hours later but rose to 72 mm. Hg in 48 hours. The aqueous again was allowed to escape and irrigation with hyaluronidase was repeated. This time the tension remained normal for six additional days without any further opening of the corneal incision.

Subsequent instillations of the enzyme were not so prolonged in effect and its use was discontinued pending further animal tests. On one occasion it was noted that the iris was apparently more friable than normal since some iris pigment was freed as the anterior chamber was irrigated. On no occasion was any opacity of the cornea noted.

Further treatment for the control of the glaucoma included a subsequent retrobulbar injection of procaine with epinephrin, cycloelectrolysis, and intravenous typhoid vaccine. The patient was discharged from the hospital on July 9, 1948, with a tension of 41 mm. Hg (Schiøtz). This gradually fell to normal in four weeks as the uveitis subsided.

The effect of hyaluronidase on the intraocular pressure of these patients demonstrated a definite beneficial action. The changes noted in the iris of each patient, however, indicated some tissue damage. In neither case was any corneal change noted. In view of the probable tissue damage, additional animal experiments were performed to determine more conclusively what changes may result and whether further clinical use is advisable.

Rabbit studies

Five groups of rabbits were used in these experiments. In the first four groups various factors such as secondary infection, impotent enzyme, and technical errors complicated the picture. Although no definite conclusions were made from the study of the animals in these four groups, certain distinctive gross changes were observed in the eyes treated with hyaluronidase.

In the fifth group of rabbits, the gross findings were conclusive and definite changes in histology were noted on microscopic examination. This last group only is reported in detail.

Procedure. A freshly prepared solution of hyaluronidase (Hyronase-Schering) containing 10 turbidity reducing units per cubic centimeter was used. An injection of 0.1 cc. of this solution was made into the anterior chamber of the right eye of each of 12 albino rabbits daily for five consecutive days. Topical anesthesia with pontocaine hydrochloride was used. The injection was made

with a 27-gauge needle to prevent leakage at the site of corneal puncture. Some aqueous was drawn into the needle before making the injection to insure adequate mixing of the enzyme.

The left eyes of the same rabbits were injected each day with 0.1 cc. of 0.85-percent sodium chloride solution as a control.

Both eyes were enucleated on the sixth day.

Gross findings

At the time of making the fourth and fifth intraocular injections it was noted that the conjunctiva of several eyes receiving hyaluronidase was quite friable. In no instance was this friability seen in a control eye.

Changes in the control eyes were mild and infrequent (table 1). A clouding of one third or one fourth of the cornea in the immediate area of the injection site (fig. 1) occurred in four eyes. Two of these developed a keratectasia. This was probably a result of an infiltration of saline into the corneal stroma during or after the injection. A transient iritis was observed in a few instances.

TABLE 1

EFFECTS OF DAILY SALINE INJECTIONS FOR FIVE DAYS

Rabbit	Time After Initial Injection				
	24 hr.	48 hr.	72 hr.	96 hr.	120 hr.
1					
2					
3		•?			
4					
5	•?			C	C ⅓
6					
7					C K ⅓
8		•			• C
9					
10					C K S
11		•			
12					

Symbols: • = Iritis; K = Keratectasia; C = corneal clouding; ⅓ = third of cornea.
Degree: Mild = Symbol only; Moderate = M; Severe = S.

Iritis in an albino rabbit is easily seen. Increased vascularization is evident by a deepening of iris color, and congestion is revealed by a purplish hue of the iris in contrast to the normal pink. Exudation is a common manifestation. The flashing of light in the eye may demonstrate the presence of synechias.

Gross changes in the hyaluronidase-treated eyes appeared early in the course of injections, and were severe (table 2). Corneal clouding (fig. 1) was observed in all eyes after the fifth injection. The opacity of the cornea varied in density but, in the overwhelming majority, obscured the iris details. Keratectasia was present in 7 of the 12 eyes. Iritis appeared in 10 of the eyes after the second injection and, in most instances, persisted throughout the injections. Only one eye did not seem to have iritis on the final day.

Histologic findings

Celloidin sections were prepared from the enucleated eyes. The staining technique of Hotchkiss[6] was used to demonstrate the polysaccharides. Hematoxylin was chosen as a counterstain.

Cornea. A diffuse swelling of the entire cornea was noted in all eyes receiving the enzyme. Only a few of the control eyes showed any swelling, and this was confined to the region of the injection where saline had infiltrated the corneal stroma (figs. 2, 3, and 4). The corneas of the treated eyes varied in thickness from 2 to 3 times that of the controls, and the normal contour was lost in many eyes. In some sections, long finger-like extensions of the anterior surface of the cornea were seen. We feel that these occurred during fixation of the softened cornea because they were large enough to have been

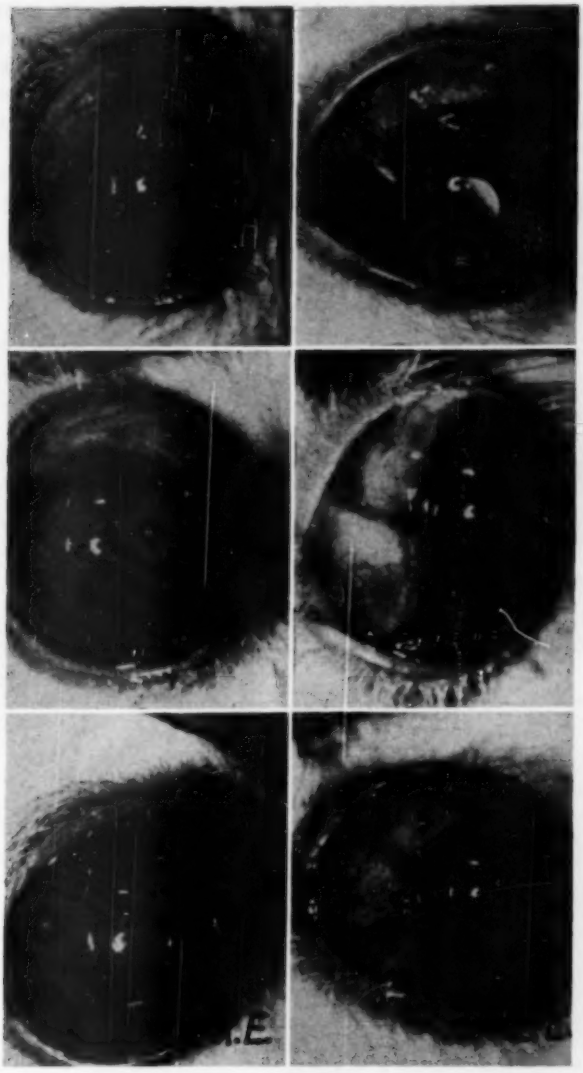

Fig. 1 (Linn and Ozment). The right eyes show the diffuse corneal clouding seen in all eyes receiving hyaluronidase. The left eyes have no corneal clouding except around the site of the saline injection.

seen grossly and probably would have been noticed at the time of enucleation.

The corneal epithelium was increased in thickness in about half of the eyes. This increase was the result of swelling of the cells rather than an increase in number of layers.

Bowman's membrane was difficult to distinguish from stroma of the rabbit cornea so no conclusions could be made specific for this membrane. It apparently was affected in the same manner as the lamellar fibers.

The substantia propria of the cornea

showed the most profound changes. It took only a faint stain in most instances which suggests a loss of polysaccharide elements. The edema was marked and certain areas revealed a complete loss of lamellar structure as though the corneal lamellae had been dissolved.

The nuclear elements of the stroma became rounded and were much more prominent. The normally flattened nuclei of the corneal corpuscles increased in length and width, some sections showing them to be of almost equal width in all directions. Other cells were found which were not identified but which resembled neurons.

Some round-cell infiltration occurred but this was not prominent except at the injection site. Nuclear elements in general were easily seen because of their increased size and the better contrast obtained in the faint-staining stroma.

Descemet's membrane. No consistent changes in Descemet's membrane and the endothelium were seen. A few sections showed a partial loss of Descemet's membrane which could have been artefact. Round-cell deposits on the endothelium were seen in half of the eyes and, in two instances, well-formed keratic precipitates were found composed of clumps of lymphocytes.

Iris. A generalized swelling of the iris to as much as twice the normal thickness was

TABLE 2

EFFECTS OF DAILY HYALURONIDASE INJECTIONS FOR FIVE DAYS

Rabbit	Time After Initial Injection				
	24 hr.	48 hr.	72 hr.	96 hr.	120 hr.
1	•	• C	• M C M	• M K C M	• M K C S
2		• C	• M C M	• S C S	• S C S
3		• C	• M C M	• M K C M	• S K C S
4	•	• M	• M	• M K C S	• S C S
5		•	• M	• M K C S	• S K S C S
6		C S	• M K C S	•	• C
7	C	•	• M C S	• M C S	• M C S
8		•		• M C S	• S K C S
9			• M	K C M	K C S
10		•	• S	• M K C S	• M K S C S
11		•		• M K C S	• M K C S
12		• S C S	• S C S	C S	• M C S

Symbols: • = Iritis; K = Keratectasia; C = corneal clouding; ⅓ = third of cornea.
Degree: Mild = Symbol only; Moderate = M; Severe = S.

noted (figs. 5 and 6). The iris took a lighter stain throughout and there was an apparent loss of stromal fibers. These changes could have resulted from the massive edema. Some round-cell infiltration was also seen in a few sections but this was not a constant finding.

The iris blood vessels had become greatly dilated and, in some eyes, attained a diameter

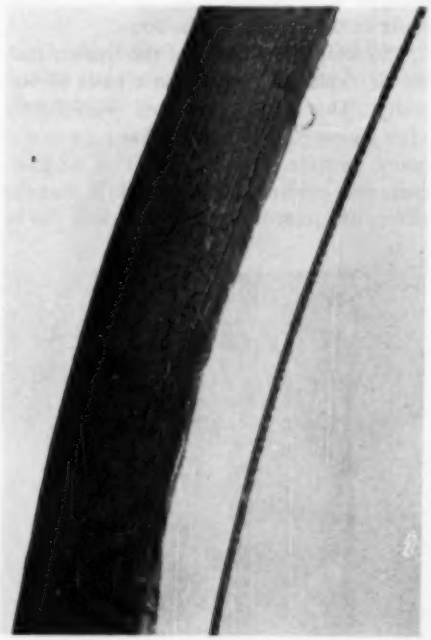

Fig. 2 (Linn and Ozment). This section represents an uninvolved area of the cornea in a control eye.

five times that of the control eye. Clumping of red blood cells in these vessels gave evidence of the congested circulation.

Firm posterior synechias were found in several eyes (figs. 7 and 8). No posterior synechias were seen in control eyes.

Ciliary processes. The ciliary processes were found to be quite swollen and congested

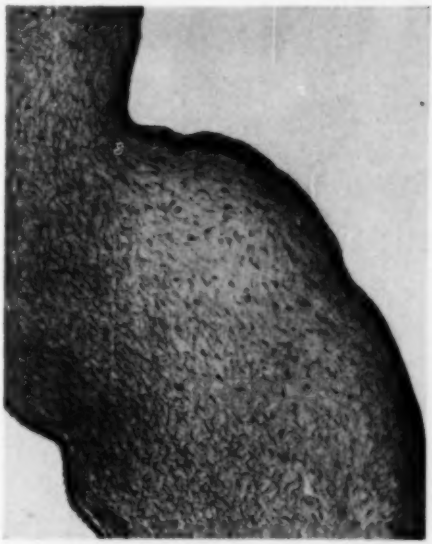

Fig. 3 (Linn and Ozment). The area of cornea infiltrated with saline at the other end of the same section shown in Figure 2. Note the massive edema with only mild change in actual tissue structure.

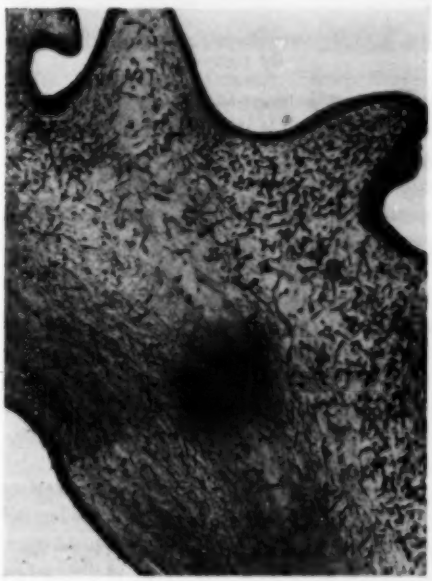

Fig. 4 (Linn and Ozment). The cornea of the hyaluronidase-treated eye of the same rabbit as in Figures 2 and 3. Note the fingerlike projections, cellular infiltration, and total loss of lamellar structure of part of the stroma.

Fig. 5 (Linn and Ozment). Section of the iris in the control eye.

(fig. 9). The blood vessels were filled with cells indicative of the stagnation of circulation. The ciliary body as a whole was not considered because such a structure comparable to that found in the human does not exist in the rabbit.

Angle of the anterior chamber. The chamber angle of the rabbit differs so much from that of the human that few conclusions can be drawn that have any application. Some sections showed round-cell infiltration and others, polymorphonuclear infiltration. The latter, no doubt, indicated secondary infection.

Anterior chamber. A fibrinous exudate containing a few round cells was found in the anterior chamber of half of the treated eyes. This exudation did not occur in the saline controls.

Comment

The hyaluronidase used in the rabbit experiments was 10 times the concentration of that instilled into the anterior chamber of our patients. This probably explains the absence of corneal changes in these patients. Although both patients exhibited changes in the iris, one cannot state to what degree these changes were produced by the enzyme because of the severity of the iritis.

The temporary effect on the tension cannot be explained entirely on a basis of viscosity. The aqueous formed immediately after a paracentesis no doubt has a lower viscosity. In spite of this, no effect on the glaucoma was evident. It is more likely that the effects of hyaluronidase in these cases can be

Fig. 6 (Linn and Ozment). Section of the iris in the treated eye. The swelling of the iris and dilation of the iris blood vessels were not as striking in all eyes as they were in the eyes of the animal represented by the section here and the section in Figure 5 (×110).

explained on a purely chemical basis. If viscosity were important, one would expect a gradual rise of intraocular pressure to occur after the enzyme effects had disappeared. In one of our patients (Case 2) the tension, after remaining normal for several days, rose suddenly in a few hours. A rise of 36 mm. was noted in a six-hour period.

The definite tissue changes noted in the rabbits certainly cause one to hesitate to make any further clinical studies until a safe dosage and mode of administration have been determined.

Fig. 7 (Linn and Ozment). Section showing posterior synechia in rabbit receiving hyaluronidase in the anterior chamber (×55).

Fig. 8 (Linn and Ozment). Section showing posterior synechia in rabbit receiving hyaluronidase in the anterior chamber (×110).

Two rabbits in a previous group of experiments were observed for several days after the enzyme had been discontinued. Both rabbits demonstrated corneal clouding without any keratectasia at the time the injections were stopped. In a period of about 10 days the cornea in each rabbit had become completely clear and indistinguishable from that of the saline control eye.

Histologic sections of these eyes failed to reveal any significant pathology. We, therefore, feel that recovery from the effects of hyaluronidase may be complete if the changes have not progressed too far. Our most recent experiments reported here were performed primarily to determine the maximum destructive effects that may be produced.

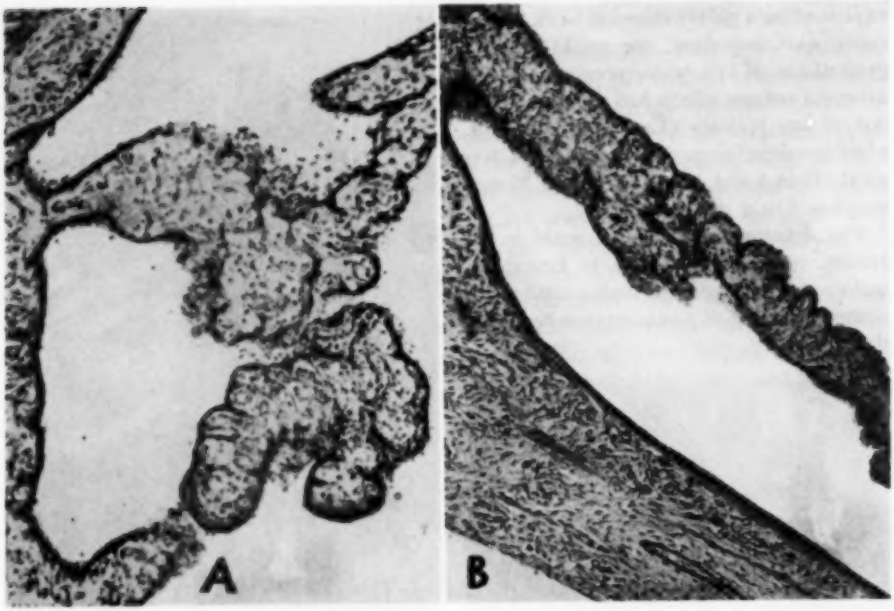

Fig. 9 (Linn and Ozment). Sections of the ciliary processes. (A) The treated eye. (B) The control eye.

We feel that hyaluronidase may prove to be important in glaucoma and that further investigations are warranted.

Summary

Hyaluronic acid and hyaluronosulfuric acid are important mucopolysaccharides found in the eye. Hyaluronidase is an enzyme having the property of depolymerizing these substances.

Hyaluronidase was instilled into the anterior chamber of two patients with secondary glaucoma and a temporary beneficial effect on the intraocular pressure was observed.

Injections of the enzyme in concentrated form into the anterior chamber of rabbits produced clouding of the cornea, keratectasia, and iritis. Histologic studies of enucleated eyes revealed destruction of corneal stroma with massive corneal edema, iritis, and congestion of the ciliary processes.

Further physiologic and chemical studies are necessary before the importance of hyaluronidase in glaucoma can be stated. Clinical use is not recommended at this time.

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We are indebted to Miss Agatha De Lacio who prepared the microscopic sections and to Mr. Albert Levin who did the photography.

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Discussion

Dr. Paul W. Miles (St. Louis, Missouri): I wish to compliment Colonel Ozment on this fine paper. I am speaking not as an authority but because a paper was read on this subject at the Midwest Section of the Association for Research in Ophthalmology in St. Louis last May. My friends, William E. Moor and Philip Shahan, read a paper on the spreading factor and its effect particularly on glaucoma. They also tried the drug on four patients.

They gave a more favorable report than did Colonel Ozment. I wonder if it might be due to the difference in preparation. Mr. Moor prepared the spreading factor himself from testicular tissues he obtained from the packing plant. He possibly used a different type of extraction from that used commercially, which may explain the differences. They used rabbits, putting India ink into the anterior chamber, observing its absorption into the angle and disappearance from the eye, showing that the spreading factor caused, I should say, about 80-percent difference in the absorption of India ink particles through the angle.

Another difference in the work of Shahan and Moor is that they emphasized not the viscosity change in the aqueous or the fluid involved, but the permeability of the cell membranes or tissue barriers in the angle. I would like to ask Colonel Ozment if that is a proper view to take toward the action of this drug?

Dr. Ludwig von Sallmann (New York): I think that this paper has many interesting aspects. Some of the points brought forward by the authors confirm observations which were made with intravitreal injection of hyaluronidase by Dr. Meyer and me on about 70 rabbits. In our series there was marked reduction in the viscosity of the vitreous several hours after a great amount of the enzyme had been introduced. As did Dr. Linn and Dr. Ozment, we also missed any regular effect of the injected enzyme on intraocular pressure. The absorption of red cells from the vitreous after the use of the enzyme was moderately increased and it could not be decided whether the result was brought about by lowering the viscosity of the vitreous jelly or by the definite toxic effect of the compound.

There are other points about which I should like to ask the authors. First, a question raised already by the previous discusser. What kind of enzyme was used, what was its degree of purification? Second, were the preparations sterile? Third, can it be excluded that the rabbits were sensitized to foreign protein by the repeated injections in case that the preparations were made from bull testes. And finally, did the authors observe permanent lesions in the cornea after injection of the enzyme in the anterior chamber? I think Dr. Braley used hyaluronidase intracorneally and might be interested in such observations.

Dr. Alson E. Braley (New York): Will you estimate the amount of polysaccharide in the cornea that disappeared after the injection of hyaluronidase? I am interested also in how the hyaluronidase was sterilized.

Dr. Jay G. Linn, Jr. (closing): First let me say that we do not consider this work as final. This is more of a preliminary study and a lot of the questions asked have occurred to us but have not been worked out as yet.

In regard to the favorability of our report, we intended to find out just how much harm could be done, and therefore we used a high concentration of the enzyme to see what we had to look for in the way of complications.

As far as permeability of the cell membranes versus the viscosity is concerned, we

started out on the viscosity theory and then reversed our opinion, deciding that viscosity wasn't quite as important as we had felt it to be originally. It is probable that permeability of the cell membranes is much more important.

The enzyme we used was not prepared by us; it was furnished to us by the Schering Corporation, prepared from bull testes, which they get from Armour. I don't know the exact details of their preparation, so I cannot answer Dr. von Sallmann's question.

In regard to the sensitivity of the protein, a good point is raised which we did not consider. However, we do not feel it is important; but certainly, before a conclusive statement could be made, that deserves further consideration.

Concerning the scars, we did have histologic sections through the injection site where there was definite scar formation, but I assume Dr. von Sallman was referring to scars residual in the opaque cornea. Although we have sections of eyes that were removed after there was a recovery from the enzyme injections, there were a few flaws in their preparation, and we are not prepared to make any definite statements on those sections. Additional sections will have to be made and some of the experiments must be repeated.

Dr. Braley's remark on the estimation of the polysaccharide content in the cornea is a good point, and we have thoughts along those same lines for future investigation.

A METHOD OF DETERMINING THE CONCENTRATION OF DITHIOCARBAMATES IN THE AQUEOUS HUMOR*

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During the recent war some reports[1] indicated that the dithiocarbamates gave promise of being an effective local antidote for liquid mustard gas burns of the eye. It was also shown that they could protect animals from death when used intravenously following lethal doses of mustard gas to the skin.[2]

The dithiocarbamates are substances with high competition factors and should, in theory, compete satisfactorily with the tissues for mustard gas provided they penetrate the cornea in sufficient concentration. As has been pointed out by others,[3] they cannot hope to influence the mustard gas already fixed in the tissue, but might be expected to combine with the still unfixed portion during the first 5 to 10 minutes.

Another way in which these compounds might work is by surface decontamination but this would have to be effected immediately while there was still a large proportion of free mustard gas on the surface of the cornea and conjunctiva. From this latter point of view they probably would not be superior to immediate irrigation with water. Hence, their main benefit would be expected to come from their early penetration into the cornea and their combination with unfixed mustard gas.

Theoretically, if high aqueous levels were obtained we would be justified in assuming

* This work was done at the Chemical Defence Experimental Station, Porton, England, in the physiological section (A. Fairley, head) and in the chemistry section (G. S. Hartley, head).

that the concentration in the cornea was as high or higher.[4] If, on the other hand, the aqueous levels were found to be low, it would be probable that the concentration in the cornea was insufficient to do any good.

In our own experiments (to be reported elsewhere) the therapeutic results were disappointing in the long run. Neither sodium diethyl dithiocarbamate nor sodium methyl ethanol dithiocarbamate afforded significant protection to the corneas of rabbits. However, in the course of the experiments, a method was developed for measuring the concentration of dithiocarbamates in the aqueous, which we consider worthwhile reporting.

Measuring dithiocarbamates in aqueous

Sodium diethyl dithiocarbamate is used commercially to detect the presence of copper, giving a brownish color when coming into contact with it. In modifying this test it was found that by adding a drop of 0.02-percent copper-sulfate solution to a sample containing sodium diethyl dithiocarbamate, a yellowish brown color was produced, the depth of which varied in direct proportion to the concentration of sodium diethyl dithiocarbamate in the sample. Thus standard solutions of known concentrations could be made up in advance and a sample of aqueous compared to them colorimetrically.

It was found necessary to use fresh, normal, pooled aqueous in making up the standard solutions since a different color was obtained with it than with water. This may have been due to the high fibrin content in rabbit aqueous. Furthermore, the color of the standard solution made with water tended to fade rather rapidly, whereas, that made with aqueous remained constant for over 24 hours.

Sodium methyl ethanol dithiocarbamate gave a more yellowish brown color and samples of this were also compared colorimetrically with standard solutions of known concentrations.

It should be pointed out that this is a "spot" test and not completely accurate. However, it served its purpose in giving a rapid determination of the approximate concentration of the dithiocarbamates in mg. per 100 cc. of aqueous.

Procedure

One eye of a series of anesthetized rabbits was contaminated with 0.0004 ml. of pure distilled mustard gas delivered by a combined microsyringe and microburette.[5] Two minutes later three drops of either sodium diethyl dithiocarbamate (40-percent solution, pH 8.0) or sodium methyl ethanol dithiocarbamate (40-percent solution, pH 8.0) were instilled into each eye, using the lake method of Scholz.[1] After 10 minutes, the eyes were carefully washed with water and aqueous punctures were made.

One drop of 0.02-percent copper sulfate solution was added to a measured amount of the aqueous sample which was then transferred to a small capillary tube of standard length.* This tube was then compared to similar tubes containing the freshly made up standards, by viewing the liquid columns vertically through the tube openings under uniform lighting conditions. A faint color could be detected more readily by this vertical view than by observing them horizontally through a glass tube itself. Concentrations as low as 0.5 mg. per 100 cc. of aqueous could be detected in this manner.

Tables 1 and 2 show that neither of the two dithiocarbamates used penetrated the cornea to any great extent as shown by the low aqueous concentrations in normal and contaminated eyes. When the eye was burned 5 or 10 minutes previous to aqueous puncture, the corneal permeability was apparently not sufficiently changed to allow increased penetration. If, however, 48 hours

* Length of tube, 10 cm.; internal bore, 2.5 mm.; length of fluid column, 8 cm.

were allowed to elapse between burning and aqueous puncture, the drugs could be recovered in large quantities. Since the only time large corneal concentrations would be useful is when there is still some unfixed mustard gas in the cornea (that is, within 5 to 10 minutes following contamination), any increased penetration after this period would not be expected to be of benefit.

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TABLE 1

LOCAL PENETRATION OF SODIUM DIETHYL DITHIOCARBAMATE

(mg./100 cc. aqueous—figures given to nearest standard)

	Eye Burned with Mustard Gas	Control
10 min. after burning	0.50	2.00
	0.50	2.00
	2.00	0.50
	5.00	5.00
	3.50	5.00
	1.50	2.00
48 hrs. after burning	50.00	2.00
	50.00	3.00

TABLE 2

LOCAL PENETRATION OF SODIUM METHYL ETHANOL DITHIOCARBAMATE

(mg./100 cc. aqueous figures given to nearest standard)

	Eye Burned with Mustard Gas	Control
5 min. after burning	0.50	1.00
	0.75	1.00
	0.50	0.50
	0.50	0.50
10 min. after burning	0.75	1.00
	0.75	0.75
	1.00	1.00
	0.75	0.75
48 hrs. after burning	85.00	0.50
	80.00	1.00

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EXPERIMENTAL STUDIES OF FATIGUE OF ACCOMMODATION. II*

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INTRODUCTION

Carmichael and Dearborn[2] recently stated that "fatigue is one of those common concepts familiar to all mankind which turn out on close inspection to be far from clear or simple." Fatigue has variously been used in scientific reports as a cause of certain results, as a description of events, and as an entity in itself. To date no evidence has been found to justify the use of the term as either an entity or as a cause. In fact the diversity of phenomena described by the term tends to invalidate such usage. In this study, then, we use the term as a description of events which occur. For the purpose of clarity we further define fatigue as impairment of function. Thus our use of such terms as ocular fatigue, decrement, recession of near point of accommodation implies an objective, measurable change in the performance of a function as a result of or following a definite work task.

In their impressive studies of visual fatigue in reading, Carmichael and Dearborn found no objective evidence of impairment during six hours of continuous reading of "light" or "heavy" materials or of microfilm projections of the same materials. Nevertheless, they did obtain reports of "tiredness," boredom and nervous tension, irritability, smarting or watering of eyes, blurred images, cramped muscles, and other similar reactions of the subject to the task at hand.

Of them, these authors stated "they may be masked in periods of unusual stimulation or motivation, and although they do not, as we must hold, in and of themselves constitute fatigue, (they) are important as indices or signals of fatigue or of its approach and of the possible depleting of energy reserves. In fact, they may be the only indications of the onset of fatigue on which we can count prior to the actual impairment of performance or reduction of output."

This formulation of the relation of physical, physiologic, and psychologic concomitants of performance to the objective occurrence of impairment provides a broad framework in which much of the scattered literature in this field may be interpreted. To quote again, it "seems to confirm the view that the total normal sensory-neuromuscular eye mechanism is remarkably resistant to fatigue in an operation such as normal reading. It must be emphasized, however, that this does not mean that fatigue of the eye mechanism cannot be brought about by abnormal means."

The present study was undertaken in an effort to correlate the fatigue of accommodation, which has been the subject of much research, with significant causative factors. A group of asthenopic patients was selected as subjects because it has previously been found that recession of the near point of accommodation occurs more readily with asthenopes.

EXPERIMENTAL DESIGN

Our previous paper[1] outlined the design of this research. Fifty-seven civilian subjects, 21 male and 36 female, ranging in age from 9 to 54 years, were tested in 12 experiments. These subjects were selected by a hospital clinic ophthalmologist for referral on the basis of symptoms of asthenopia and complaints of ocular fatigue. Patients with pathologic eye conditions or squint were not

* This study was aided by grants from the National Research Council and The Ophthalmological Foundation, Inc. Presented at the eighteenth scientific meeting of the Association for Research in Ophthalmology, Philadelphia, June, 1949.

referred. High motivation to coöperate with the research was obtained by the device of having the referring ophthalmologist inform the patients that they were to receive exercises for the eye muscles. Because of this explanation, despite boredom and the inconvenience of returning a number of times, the subjects appeared to comply with instructions and to manifest much interest in their performances.

The details of the experimental design are: Each subject was used as a control on himself in 12 experiments, in which three conditions were varied. These were: (1) Ergograph eye treatment (EET), consisting of a separate series of experiments in which the right eye was tested on the ergograph with the left eye occluded, L.E. with R.E. occluded, and a binocular series (O.U.); (2) illumination, in which half of the ergograph runs were at five foot-candles and the other half at 50 foot-candles (f.c.); and (3) test object, in which half of the ergograph runs employed a fine double-line cross as test object, and the other half employed photographically reduced letters on a Berens accommodation card.

Thus, the 12 experiments, in combination, consisted of (1) R.E., cross, 5 f.c.; (2) L.E., cross, 5 f.c.; (3) O.U., cross, 5 f.c.; (4) R.E., letters, 5 f.c.; (5) L.E., letters, 5 f.c.; (6) O.U., letters, 5 f.c.; (7) R.E., cross, 50 f.c.; (8) L.E., cross, 50 f.c., (9) O.U., cross, 50 f.c.; (10) R.E., letters, 50 f.c.; (11) L.E., letters, 50 f.c.; (12) O.U., letters, 50 f.c.

Each ergograph work period was 30 minutes, except in cases where the subject was unable to complete the task because of excessive fatigue, pain, or discomfort. Subjects wore prescribed corrections during the experiments.

Immediately before each ergograph run and immediately following each run, a series of measurements was taken for each subject. These consisted of muscle balance at 25 cm. and 6 meters, using the Maddox rod, and near point of accommodation for R.E., L.E., and O.U. These measures are designated as MB-25-I (muscle balance, 25 cm., initial), MB-6-I, NPA-RE-I, NPA-LE-I, NPA-OU-I, and the comparable final measures follow the same notation with the letter F (final) instead of I. Differences between initial and final measures are designated as decrements and follow the same notation, too, using the letter D (decrement). To distinguish references to R.E., L.E., O.U., as experimental conditions under EET from those used to designate initial and final measures, the latter will be referred to as eye measured, EM. A uniform procedure was followed for all initial and final measures, which were taken at 10 foot-candles of illumination.

Resume of previous results

The previous report of this research[1] presented the gross results concerning changes in near point of accommodation following ergograph exercise. In that report the data were measured in centimeters. Each of the 36 differences between initial and final near point means was statistically significant. This was interpreted as evidence of the occurrence of fatigue of accommodation following ergograph exercise.

In addition it was found that the decrement in eye measured (EM) was greater in each case for the eye worked (EET) than for the eye occluded in the ergograph period, although both were statistically significant. These results confirm the expectation that both eyes will manifest accommodation decrement (fatigue), even when only one works (that is, is subjected to accommodation exercise) while the other is occluded. The differential effect, however, may be attributed to the fact that for any given EET the result for the corresponding EM is direct while for the other it is a product of neuromuscular interaction of the accommodation-convergence systems.

Presentation of additional findings

Plan of the present paper

Further analysis of the data of this research was interrupted by the war. The pres-

ent paper presents a detailed analysis of the accommodative and muscle-balance data in relation to each other, to age, and to related experimental variables, such as time on ergograph before blurring out (if less than maximum time of 30 minutes) and number of decrement records per subject. In addition, we have recomputed the basic data of the earlier report. These were reported in centimeters and, while statistically impressive, are now presented in diopters in order to give a more adequate report.

Reanalysis of near point of accommodation decrements (NPA-D)

Table 1a summarizes the recomputed mean initial and final near points of accommodation and near-point decrements. For the total group of 57 asthenopes, the mean initial near points are 9.87 diopters for R.E., 9.87 for L.E., and 10.61 for O.U. The mean final near points (measured immediately following the period of ergograph exercise) are 8.82, 8.89, and 9.46 diopters, respectively. The mean decrements, in the same order, are 1.08, 0.98, and 1.15 diopters, respectively. The mean decrements are all statistically significant; that is, the probability is practically zero that they could have occurred by chance.

The supporting data for Table 1a appear in Table 1b, showing the means and standard deviations as well as the critical ratios of the difference (decrement) to the standard error of each difference for each of the 12 experiments. Table 1b corresponds to Tables 2 through 13 of our original report[1] and the results in dioptric terms are substantially the same as those previously reported in centimeters. Thus, the basic evidence of occurrence of fatigue of accommodation following ergograph exercise is confirmed for this group of asthenopic patients.

Table 2 summarizes the mean decrement data of Tables 1a and 1b to demonstrate the other finding, previously reported in centimeters, of the effect of ergograph exercise of one eye on fatigue of the other, occluded eye.

Each figure in Table 2 is the average of the corresponding mean NPA-D for four experiments. For example, the mean decrement for EM-RE and EET-RE is the average of the corresponding mean EM-RE for Experiment 1 (R.E.—cross, 5 f.c.); Experiment 4 (R.E.—letters, 5 f.c.); Experiment 7 (R.E.—cross, 50 f.c.) and Experiment 10 (L.E.—letters, 50 f.c.).

Table 2 indicates that the decrement for the eye measured corresponding to the ergograph eye treatment (working eye) is greatest in each case, exceeding that of the occluded eye or O.U. From Table 2 this difference can be computed; it represents an average of 0.39 diopters.

TABLE 1A

Summary of mean initial and final near points and near-point decrements for all experiments*

Eye Measured	Mean Initial Near Point (NPA-I)	Mean Final Near Point (NPA-F)	Mean Near-Point Decrement (NPA-D)
R.E.	9.87	8.82	1.05
L.E.	9.87	8.89	0.98
O.U.	10.61	9.46	1.15
Total	10.11	9.05	1.06

* No. = 57. Data in diopters.

Individual differences in accommodative decrement

Notwithstanding the fact that the mean decrements for the total group are statistically significant, an analysis of individual records reveals a wide range of individual differences among the 57 patients tested. Of the total of 2,052 decrement measures (for 57 subjects with 36 measures each), only 1,226, or 60 percent, were positive, while 18 percent showed no change, and 22 percent an increase in accommodation near point. Only three subjects obtained a positive decrement on all 36 measures.

At the other extreme, one patient had only four positive decrements, with no change on eight measures, and an increase in accommodation on 24. The range of individual dif-

ferences found is shown in Table 3, which classifies the cases according to the frequency of positive decrements (loss of accommodation). The distribution ranges from 14 patients (24 percent of group) with an average of 33 positive decrements through a gradual progression to one patient with only four.

The explanation of these individual differences is one of the main purposes of this study. Pathologic factors and squint were eliminated experimentally in the selection of cases for referral. It is presumed that each of our subjects was an asthenope, which implies that to some extent psychologic factors are involved in the etiology. However, no

TABLE 1B

COMPARISON OF INITIAL AND FINAL MEAN NEAR POINTS OF ACCOMMODATION
Experiments 1 through 12*

Exper.	Experimental Conditions	EET	EM	Mean NPA-I	S.D.	Mean NPA-F	S.D.	Mean NPA-D	Critical Ratio
1	Cross 5 f.c.	R.E.	R.E.	9.94	2.00	8.32	2.71	1.62	5.05
			L.E.	9.72	2.35	8.89	2.90	0.83	2.65
			O.U.	11.05	2.22	9.83	2.80	1.22	3.30
2	Cross 5 f.c.	L.E.	R.E.	9.89	2.33	8.95	2.93	0.94	3.64
			L.E.	9.75	2.10	8.33	3.02	1.42	5.08
			O.U.	10.76	2.67	9.97	3.10	0.79	2.90
3	Cross 5 f.c.	O.U.	R.E.	9.74	1.92	8.88	3.02	0.86	3.09
			L.E.	9.87	2.18	8.96	3.33	0.91	3.07
			O.U.	10.74	2.50	9.01	3.31	1.73	4.79
4	Letters 5 f.c.	R.E.	R.E.	9.65	2.07	8.39	2.96	1.26	4.29
			L.E.	9.96	2.56	8.91	2.87	1.05	4.07
			O.U.	10.65	2.58	9.42	2.91	1.23	4.78
5	Letters 5 f.c.	L.E.	R.E.	9.47	2.13	8.48	2.51	0.99	3.73
			L.E.	9.50	2.24	8.16	2.75	1.34	4.50
			O.U.	10.16	2.33	9.44	2.99	0.72	2.21
6	Letters 5 f.c.	O.U.	R.E.	9.76	2.13	9.09	2.60	0.67	2.41
			L.E.	9.74	2.25	8.92	2.66	0.82	2.82
			O.U.	10.25	2.41	8.97	2.80	1.28	3.85
7	Cross 50 f.c.	R.E.	R.E.	9.64	2.05	8.69	2.91	0.95	3.33
			L.E.	9.64	2.08	8.99	2.97	0.65	2.18
			O.U.	10.48	2.13	9.33	3.05	1.15	3.78
8	Cross 50 f.c.	L.E.	R.E.	10.00	2.38	9.01	3.13	0.99	3.04
			L.E.	9.79	2.26	8.78	3.25	1.01	3.29
			O.U.	10.46	2.30	9.59	3.32	0.87	2.55
9	Cross 50 f.c.	O.U.	R.E.	10.03	2.35	8.98	3.16	1.05	3.76
			L.E.	9.98	2.29	9.08	3.27	0.90	2.48
			O.U.	10.55	2.40	9.33	3.77	1.22	3.36
10	Letters 50 f.c.	R.E.	R.E.	10.10	2.34	8.82	3.20	1.28	4.34
			L.E.	10.21	2.34	9.35	3.29	0.87	3.03
			O.U.	10.73	2.29	9.78	3.23	0.95	3.19
11	Letters 50 f.c.	L.E.	R.E.	10.06	2.29	8.94	2.64	1.12	4.30
			L.E.	10.13	2.46	8.88	3.11	1.25	4.66
			O.U.	10.67	2.34	9.37	2.54	1.30	5.28
12	Letters 50 f.c.	O.U.	R.E.	10.18	2.42	9.32	3.04	0.86	3.30
			L.E.	10.11	2.40	9.40	3.32	0.71	2.66
			O.U.	10.78	2.32	9.46	3.35	1.32	4.40

* No. = 57. Data in diopters.

psychologic examinations were made and classification of patients in relation to psychoetiology is not possible.

Data are available and will be analyzed on the relation of accommodation decrement to initial near point of accommodation, refractive error, age, muscle balance at near and distance, and concomitant change in lateral phorias following ergograph exercise. It will be shown that, at least so far as these experiments are concerned, none of these factors is significantly causally related to accommodation fatigue.

Clinically related indicators of accommodation fatigue

It will be noted in Table 3 that the mean total decrement in diopters for each group varies with the number of positive decrements. The correlation of the number of positive decrements with the total measured decrement in diopters is 0.89. Thus the direction of change is highly associated with the amount of fatigue decrement and may be used clinically as an indicator of fatigue for ergograph exercises.

Furthermore, as shown in Table 4, the correlation of number of positive decrements (loss of accommodation) with negative decrements (gains) is −0.89 and with zero decrements (no change) −0.75, while negative and zero decrements have a positive correlation of 0.46. Thus, clinically, the negative and zero decrements should be grouped together as evidences of no fatigue and opposed to the positive decrement which signifies recession of the near point or loss of accommodation.

TABLE 2

Summary of mean near-point decrements by EM and by EET*

Ergograph Eye Treatment	Mean Decrement in Diopters: Eye Measured		
	R.E.	L.E.	O.U.
R.E.	1.28	1.01	0.85
L.E.	0.86	1.25	0.83
O.U.	1.13	0.92	1.42

* Each figure is the average of four experiments. No. = 57. Data in diopters.

TABLE 3

Distribution of cases by number of plus, minus, and zero decrements and total decrement in diopters for corresponding cases*

No. of Plus Decrements	No. of Cases	% of Group	Mean No. of Decrements			Mean Total Decrement in Diopters
			Plus	Zero	Minus	
Over 30	14	24	33	2	1	88.2
25–30	9	15	27	4	5	75.3
20–25	10	17	22	7	7	40.5
15–20	8	14	18	6	12	19.5
10–15	11	19	11	12	13	− 9.9
5–10	4	7	6	12	18	−33.9
Under 5	1	2	4	8	24	−55.2

* Number of decrement measures per case −36. No. = 57.

TABLE 4

Correlation of total decrement in diopters with number of plus, minus, and zero decrements

	2	3	4
1. Total decrement in diopters	0.89	−0.85	−0.64
2. Number of plus decrements		−0.89	−0.75
3. Number of minus decrements			0.46
4. Number of zero decrements			

Although the total time for each ergograph run was 30 minutes, many were terminated before that time at the subject's request, be-

cause of complaints of constant blurring of the test object over the entire range of travel, extreme and painful eyestrain, headache, or similar reason.

The reasons given were analyzed but were found too unreliable for any analytical purpose. However, the time for each run was recorded. We computed the total time for 12 experiments per subject, for which the maximum would be 360 minutes. The mean total time for the entire group is 220.12 minutes, with a standard deviation of 60.47. None of the group was able to run for the entire time, although one attained a total of 340 minutes and six were over 300 minutes.

The correlation of total time with total decrement in diopters is −0.41, which indicates that the amount of time a patient can persist in constant visual pursuit of the test object is negatively associated with tendency to fatigue. Hence, it may be expected that "endurance time" on the ergograph is clinically an associated indicator of accommodation fatigue. Time also has a correlation of −0.35 with age, which suggests that the norm for younger patients should be lower than that for older ones. The significance of time as an indicator, however, depends upon having high motivation and compliance by the subject, as in these experiments.

Relation of near point of accommodation to near point decrement and to age

That accommodative power declines with age is well known. For the present group, the correlation of initial mean near point of accommodation, with age is as expected: R.E., −0.54; L.E., −0.53; O.U. −0.53. The relation of accommodative power to accommodation fatigue and of accommodation fatigue to age have been computed. The correlations of total initial near points (NPA-I) with corresponding decrements (NPA-D) are as follows: R.E., −0.09; L.E., −0.20; O.U., −0.13. None of these is statistically significant. The correlations of NPA-D with age are: R.E., 0.05; L.E., 0.06; O.U., 0.11.

Although the signs for both sets of coefficients are consistent with expectation, neither are statistically significant and no causal relations may be imputed. It is concluded, then, that for this group of asthenopes, fatigue is unrelated either to accommodative power or to age.

It is of interest to note that the above relationships were computed using centimeter as well as dioptric measures of near point of accommodation decrement. The correlations, based on centimeters are of the same sign, but are all higher and statistically significant. The dioptric values are related to absolute distance in a curvilinear manner and tend to correct for the distortions in focal length which appear in the linear centimeter scale.

Relation of accommodation decrement to refractive error

To investigate a possible relation of near-point decrement to refractive error under cycloplegia, the total decrement score for each subject (representing the algebraic score of all 36 individual decrement measures) was arrayed in descending order from greatest to least decrement. The refractive findings were then tabulated for each subject. No relation was found. Inasmuch as all subjects were tested wearing prescribed corrections it is possible only to suggest that accommodative fatigue is not correlated with refractive error when adequate correction is worn.

Relation of accommodation decrement to muscle balance

Correlations were computed between muscle-balance measures and near-point decrement. To obtain a quantitative measure of lateral phorias the following procedure was used:

Esophoria was considered as a negative deviation, orthophoria as zero deviation, and exophoria as positive. Scores were computed in prism diopters taking the algebraic sign into consideration. For ease of handling, 100

TABLE 5

MEAN AND STANDARD DEVIATIONS OF MUSCLE BALANCE SCORE DISTRIBUTIONS AND MEAN EQUIVALENTS IN PRISM DIOPTERS

	MB-25-I	MB-25-D	MB-6-I	MB-6-D
Mean	105.32	100.75	96.32	99.47
S.D.	43.95	9.13	28.20	8.42
Mean equivalents in prism diopters	0.44 Ex.	0.06 Ex.	0.31 Es.	0.04 Es.

was added to each score. Thus a score of 100 means orthophoria, below 100 esophoria, and above 100 exophoria.

A muscle-balance decrement was computed in the same manner as for near points by subtracting initial muscle balance score from final. Hence we have four average muscle balance measures, each of which represents the aggregate of 12 experiments: MB-25-I, MB-25-D, MB-6-I, MB-6-D. The means and standard deviations of these measures and the mean equivalents in prism diopters are given in Table 5.

Thus (dividing 5.32 by 12) the mean initial muscle balance at 25 cm. is equivalent to 0.44 prism diopters of exophoria and at 6 meters it is 0.31 prism diopters of esophoria. The difference between the two initial muscle-balance means is greater than that between medians, which are 99.40 (0.05 Eso.) and 97.47 (0.21 Eso.) respectively.

The higher mean of the M-25-I distribution is caused by seven scores above 160, which are above the range of the other distribution. The mean differences indicate less than 0.05 prism diopter of mean net change, although the range of variations is fairly large. The correlation between MB-25-I and MB-6-I is 0.81, which indicates a high relationship between the two among these subjects.

The correlations between muscle-balance measures and near-point measures are presented in Table 6. None of these correlations is significantly different from zero and it is concluded that no causal relations exist between muscle balance and accommodation.

ANALYSIS OF MUSCLE-BALANCE DATA

We have already described the method employed for quantitative analysis of lateral phorias. Vertical phorias have not yet been analyzed. The distribution of the entire group with respect to average initial muscle balance scores is given in Table 7.

Both distributions are fairly symmetrical and contain approximately equal numbers of esophoric and exophoric cases. However, the range of exophoria is curtailed when measurements are at six meters distance as contrasted with 25 centimeters. It appears that this is more probably a function of the method of testing than a significant difference in true muscle balance. The lateral adjustment is probably more marked at the near point.

It has already been shown that both initial and decrement muscle-balance and accommodation measures are unrelated. The cor-

TABLE 6

CORRELATIONS BETWEEN MUSCLE BALANCE AND ACCOMMODATION NEAR-POINT MEASUREMENTS

	NPA-I			NPA-D		
	R.E.	L.E.	O.U.	R.E.	L.E.	O.U.
MB-25-I	0.03	0.03	0.05	−0.02	−0.10	−0.003
MB-25-D	0.11	0.11	0.13	0.14	0.09	0.19
MB-6-I	−0.01	−0.03	−0.01	0.08	0.004	0.11
MB-6-D	0.04	0.04	0.01	−0.08	−0.10	0.01

TABLE 7

DISTRIBUTION OF INITIAL (LATERAL) MUSCLE BALANCE AT 25 CENTIMETERS AND SIX METERS

	Muscle Balance Score	Equivalent Value in Prism Diopters	MN-25-I	MB-6-I
	210–219	9.13–9.02	1	
E	200–209	8.33–9.08	1	
X	190–199	7.50–8.25	2	
O	180–189	6.67–7.42	2	
P	170–179	5.83–6.58	0	
H	160–169	5.00–5.75	1	
O	150–159	4.17–4.92	2	1
R	140–149	3.33–4.08	1	3
I	130–139	2.50–3.25	4	4
A	120–129	1.67–2.42	3	4
	110–119	0.83–1.58	5	5
	100–109	0–0.75	6[1] Mdn	10[2] Mdn
E	90–99	0.83–0.08	8 99.40	11 97.47
S	80–89	1.67–0.91	5	5
O	70–79	2.50–1.75	6	6
P	60–69	3.33–2.58	2	3
H	50–59	4.17–3.41	3	4
O	40–49	5.00–4.25	2	0
R	30–39	5.83–5.08	1	1
I	20–29	6.67–5.91	2	1
A				

[1] Includes one score of 100.
[2] Includes two scores of 100.

TABLE 8

RELATION OF MUSCLE BALANCE DECREMENT TO INITIAL PHORIA (25 CM.)

Initial Average MB-25 Score	Equivalent Individual Phoria Score (in prism diopters)	N	Net Change			
			Positive		Negative	
			N	Average Change	N	Average Change
150 Over	Over 4.2 Ex	9	8	10.0	1	6.0
120–150	1.7 to 4.2 Ex	8	3	13.8	5	6.4
100–120	0 to 1.7 Ex	11	4	4.5	7	2.8
80–100	1.7 Es. to 0	13	7	3.7	6	4.5
50– 80	4.2 Es. to 1.7 Es.	11	6	10.0	5	7.0
Below 50	Over 4.2 Es.	5	1	1.0	4	12.8

TABLE 9

RELATION OF MUSCLE BALANCE DECREMENT TO INITIAL PHORIA (6 METERS)

Initial Average MB-6 Score	Equivalent Individual Phoria Score (in prism diopters)	N	Net Change			
			Positive		Negative	
			N	Average Change	N	Average Change
150 Over	Over 4.2 Ex.	1	0	0	1	3
140–150	3.3 to 4.2 Ex.	3	3	11.7	0	0
120–140	1.7 to 3.3 Ex.	8	8	8.0	0	0
100–120	0 to 1.7 Ex.	15*	5	4.4	6	3.5
80–100	1.7 Es. to 0	16†	8	4.0	7	4.4
50– 80	4.2 to 1.7 Es.	12	1	9.0	11	10.4
Below 50	Over 4.2 Es.	2	0	0	2	7.5

* Includes 4 cases with no change.
† Includes 1 case with no change.

relation of muscle-balance measures with age further discloses no statistically significant relationship. These correlations are as follows: with MB-25-I, −0.08, with MB-25-D, −0.02, with MB-6-I, −0.08, and with MB-6-D, 0.07.

Effect of ergograph exercise on lateral phorias

The ergograph task involves visual pursuit of the test object and is simultaneously a convergence as well as an accommodation exercise. It is expected, therefore, that an observable effect may be found in lateral phoria decrement measures.

Correlations were computed between initial and decrement average muscle-balance scores for near and distance measures. These are 0.35 for near and 0.62 for distance. The correlation between the two decrement scores is 0.51. It appears then that the two measures are related and that the effect of erograph (convergence-accommodation) exercise on lateral muscle balance is to increase the phoria in the direction of the original displacement. While the correlation coefficient for near is relatively low, it is significant. The coefficient for six meters represents a fairly high relationship.

To inquire further into the nature of this relationship we have made an analysis of individual cases. Tables 8 and 9 show the number of cases and net positive and negative change for each set of measures when the entire group is classified according to initial muscle balance. The relationships disclosed in these tables are consistent with the correlation coefficients. In both tables there are reversals, although the trend toward increase in the direction of initial phoria is clearly shown. This trend is more pronounced in Table 9 at six meters. There is a tendency for this relationship to occur more clearly with extreme cases.

An adequate explanation of this interesting result must await further study and examination of individual cases. Unfortunately, a complete ophthalmologic examination of each subject, including prism convergence and complete orthoptic data, is not available. It is planned to investigate this problem further in new experiments.

Relation of muscle-balance data to cycloplegic refractions

The muscle-balance data were arrayed and tabulated against refractive error under cycloplegia in the same manner as the near-point data, described above. No relationship was found.

Discussion

The principal contributions of this paper are: (1) Demonstration of statistically adequate evidence of a mean decrement of slightly more than one diopter in near point of accommodation, following ergograph exercise, for a group of 57 asthenopes; (2) presentation of a reliable statistical basis for the development of a clinical test of ocular fatigue; (3) the elimination of refractive error, age, accommodative power, muscle balance (lateral phoria), and muscle-balance decrement as causal factors related to fatigue of accommodation; (4) the tendency for ergograph exercise to affect lateral phorias by increasing the original phoria in the same direction. These are discussed in turn below.

1. Accommodation decrement

The method employed in this study, of computing accommodation decrement in terms of the difference between initial and final near-point measures, differs from other ergographic studies in which evidence of impairment was based on the shape of the "fatigue curve." While in our own data the shape of the kymograph tracing does correlate positively with the measured decrement, there is an important difference between the two methods.

There are occasions in which a subject with high motivation may maintain a high level of performance with relatively little recession of near point during the ergograph period, only to have a considerable recession,

as though by relaxation from the tension of the work period, immediately after.

There are other cases, which appear to have a constant recession throughout, followed by no change or an increase in accommodation when measured immediately after stopping the ergograph. The latter case might illustrate "adaptation."

The use of the ergograph data directly may then represent more the subject's method of adapting to the work situation, as an expression of his motivation and desire to comply with instructions, than a true measure of the amount of impairment caused by the work itself.

On the other hand, the difference between two measures separated by a period of interpolated work shows more directly the effect of the work on ability to perform. This advantage of our method appeared particularly when a subject stopped before maximum time because of head pain or back pain, but was able to accommodate a moment later after changing body position.

Our data do not permit an adequate analysis of subjective feelings correlated with objective performance. Many individual sessions were terminated before the scheduled 30-minute time limit. Reasons stated were "my head hurts," "I feel tired all over," "I can't see anything at all," and the like. However, when an attempt was made to classify these reasons it was felt that they were too unreliable for use.

The objective recording of time until stopping is correlated with subjective feeling, but it is difficult to interpret whether the reason for stopping is general body discomfort, boredom or impatience to end a disagreeable task, or true impairment of accommodative function.

The experimental procedure of inserting a +1.0D. lens before stopping served to eliminate retinal adaptation and no confusion results from that source. Concerning time, it has been found that it does correlate negatively with total decrement and, if assurance of appropriate motivation is present, it may be considered as "endurance time," with general reference to interfering subjective factors.

2. Statistical basis for clinical tests

It has been shown that direction of change in near point of accommodation following ergograph exercise correlates very highly with the amount of measured decrement. Endurance time correlates negatively with amount of decrement. On the basis of these facts it is possible clinically to measure fatigue of accommodation without the use of elaborate equipment. Suggestions for a clinical test, based on the data obtained in this study, will be included in a later paper.

3. Elimination of probable causal factors

The mean near point of accommodation decrements for the entire group were found to be statistically significant. Nevertheless individual differences of considerable magnitude were found. Analysis of the relation of decrement measures to refractive error, age, initial near point of accommodation (accommodative power), muscle balance, and muscle-balance decrement indicated a consistent lack of correlation. It may, therefore, be concluded that none of these factors nor pathologic conditions, nor squint, which were experimentally excluded, is related to or is causally involved in fatigue of accommodation.

In view of these findings, the factors of motivation and psychologic or psychoneurotic mechanisms may be cited as unexplored causative hypotheses. Unfortunately, however, our data do not permit analysis of either of them and they must be deferred for further research.

4. Effect of ergograph exercise

Our findings concerning the effect of ergograph exercise on lateral phorias should be considered as suggestive and subject to verification upon repetition of a similar experiment. In our opinion the measurement of

phorias is less reliable than that of accommodation and the reliability of our phoria measurements is not known. The trends observed, for initial phorias to increase in the initial direction following ergograph exercise, are clear, although several reversals are apparent in Tables 8 and 9. These results are significant if verified and are being repeated in a new study.

Conclusion

The explanation of individual differences in accommodative fatigue among patients without obvious pathologic conditions or squint, all of whom were referred by a clinic ophthalmologist with complaints of eyestrain and eye pain and diagnosed as asthenopes, remains unsolved in this study after eliminating most relevant measurable factors. Unfortunately motivation, which is suspected, cannot be measured. The importance of securing some tangible personal assurance of maximum effort from every patient cannot be overemphasized.

No attempt was made in this group of patients to study certain factors (anemia, hypothyroidism, chronic sinusitis, chronic colitis, and so forth), which apparently have been related to fatigue of accommodation in some cases in the clinical and ergographic study of more than 3,000 patients. Therefore, these and other physical factors cannot be eliminated as possible causes of fatigue in this group of asthenopic patients.

Finally, from the results of this study the need for careful research on the relation of personality structure and neurotic mechanisms to eye fatigue and asthenopia is emphasized. Such a study, in the field of psychosomatic ophthalmology, is urgently needed.

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Discussion

Dr. Walter B. Lancaster (Boston): I want to compliment the essayist for his perseverance in this field, going back more than 30 years, and his final demonstration of the correlation which he is attempting to prove.

I should like to say that as far as non-asthenopic patients are concerned, or normal individuals, the essence of any test of fatigue by the performance of work, pretty clearly demonstrated by Mosso and his successors, is this: if the work to be done is below a certain threshold, that muscle can go on working indefinitely. In order to show fatigue, the work done must exceed a certain minimum.

When Dr. Williams and I attempted to apply Mosso's principle, we tried a test of moving the object forward and backward. We found no falling off. We then decided that a more severe test must be applied in order to produce fatigue, and that severe test was holding the object just inside the near point; and there, instead of falling off, we found the accommodation increased.

The essence of any method of testing fatigue is that the work done must exceed a certain minimum.

Dr. Williams and I established, beyond any possibility of doubt, that for ordinary individuals this test demands less than the minimum required to produce fatigue. It will not show fatigue except in pathologic cases.

Dr. Wilhelm Buschke (New York): I should like to ask Dr. Berens if he has made any observations on recovery from fatigue

of accommodation, which would be perhaps in any way comparable with the observations of Loewenstein on the recovery from fatigue of the pupil. In these pupillographic observations where the response was first exhausted by repeated light stimuli, instantaneous restitution of response to light was elicited by extraneous stimuli, such as acoustic stimuli or emotional stimuli. I think those aspects of recovery from fatigue would be particularly interesting from the standpoint of their possible psychosomatic implications.

DR. CONRAD BERENS (closing): As always, Dr. Lancaster has put his finger on the most important point that the work done must exceed the ability of the mechanism of accommodation to adapt if fatigue is to be demonstrated.

I do not know whether I made sufficiently clear the difficulty we had in fatiguing accommodation. We have tried many different methods. In the machine I showed you there is a hand lever so that one can keep the test object always at or just within the near point of accommodation. We name graphs produced in this manner continuous effort graphs, although, in a sense, the so-called repeated effort graphs are also continuous effort as complete relaxation is not permitted.

I did not go into detail about the various types of test objects we used. In this particular test we used photographically reduced print, which we found was really better than the fine crosses. We also used the fine double-line cross, which was the test object worked out in the Department of Physiology at Columbia some years ago, and we found that to be the best in the series of test objects we made at that time for studying the near point of accommodation.

We did not speak today of the fact that, in administering this test, you must have the person look from one letter to another or from one part of the cross to another in order to prevent so-called retinal adaptation. Another way of excluding this as a factor is by adding a plus 1.0D. sph. when there is blurring out of the test object, or by using a 1.5-mm. pinhole and to see whether the subject can still accommodate.

In order to make these subjects show fatigue, we had to give them a short recession. You saw that, in the work Dr. Lancaster did in the graph I demonstrated, the particular subject he used showed approximation of the near point at first and later recession of the near point which he stated indicated fatigue.

Dr. Lancaster also brought out some important points in regard to the way the lens slowly adjusts itself. He pointed out that probably there was not merely muscular action but also a slow reaction of the lens to the contraction of the ciliary body. As a matter of fact, his observations made back in 1914 have stood the test of time and are still our standard.

The question raised by Dr. Buschke is exceedingly important, that is, whether we have any evidence of recovery from fatigue. I think the most striking evidence that I obtained was observed in 1918 when performing fatigue tests in the low-pressure chamber. On a so-called normal subject the test is performed first at sea level and he will run a perfectly flat graph with no evidence of fatigue. (We have published these graphs.) Then place him at 22,000 feet in the low-pressure chamber and the graph will show a curve like the one we showed you of the man who fatigued in three minutes. That was just about the type of graph we obtained in the low-pressure chamber. At sea level the graph will flatten out and appear like the pre-anoxia test.

Therefore, although we consider psychologic factors important in this group of asthenopic patients, we do place considerable reliance on the appearance of these graphs in evaluating fatigue of accommodation with the ergograph which we used in making these studies.

EFFECTS OF METABOLIC POISONS AND OF SOME OTHER AGENTS ON INTERCELLULAR COHESION IN CORNEAL EPITHELIUM*

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Intercellular cohesion is one important criterion of tissue organization. Changes of cohesion can be either transitory or permanent, and loss of cohesion has been observed in certain functional states of normal tissues[1,2] as well as in malignant epithelial growth.[3-5] The healthy, uninjured corneal epithelium is an example of an organized tissue, but it may be expected to lose—at least temporarily—some of its organization following injury and during wound repair.

Previous observations on the mode of cell movements following various types of injuries to corneal epithelium suggested that intercellular cohesion may be an important variable affecting the mode of cell movements in the process of healing.[6] A study of factors concerned in cell cohesion in this tissue should, therefore, be of interest both from the special standpoint of wound healing, and from the more general one of tissue organization.

In a previous investigation[7] semiquantitative methods for testing intercellular cohesion in sheets of corneal epithelium have been described. With these methods, the effect on cohesion of various enzymes and of some other agents has been studied. It was found that some proteolytic enzymes (chymotrypsin, trypsin, papain) induced loss of cohesion without any marked interference with morphologic cell-integrity. In contrast, ribonuclease, hyaluronidase, and a lecithinase were found to have no effect on cell cohesion. In addition, we found recently that β-glucuronidase has no effect on cell cohesion in a concentration of approximately 250 units per ml. of solution and at a pH of 4.5.†

The striking effects on intercellular cohesion, produced by some proteolytic enzymes in low concentrations, suggested the possibility that proteolytic enzymes present in the tissue may play a role in physiologic and pathologic variations of cell cohesion. However, an overall decrease of cell cohesion may—in the normal living tissue or in surviving tissue in vitro—be obscured by simultaneous processes of protein synthesis, and these are likely to require metabolic energy. Interference with energy yielding or energy transferring metabolic processes may, therefore, be expected to let the effects of intrinsic proteolytic activity in the tissue become manifest. In the present study, intercellular cohesion was examined following exposure of the tissue to various metabolic inhibitors and to some other substances of biologic interest.

MATERIALS AND METHODS

The experiments were performed on beef corneas.‡ The eyes arrived in a cooled container about three hours after the animals had been killed. Care was taken to select for the experiments eyes which were free from erosions. The experimental solution to which the tissue was to be exposed was injected

* From the Ayer Foundation Ophthalmic Research Laboratory, Manhattan Eye, Ear, and Throat Hospital. This investigation was supported in part by a research grant from the National Cancer Institute, U. S. Public Health Service. Presented at the eighteenth scientific meeting of the Association for Research in Ophthalmology, Philadelphia, June, 1949.

† Samples of β-glucuronidase and of the phenolphthalein-glucuronide used in assaying the activity of the enzyme preparations[8] were kindly supplied by Dr. William H. Fishman, Cancer Research Unit, Tufts College Medical School, Boston, and by Dr. Bernard Becker, Wilmer Institute, The Johns Hopkins Hospital, Baltimore.

‡ The generous coöperation of the American Packing Corporation, Jersey City, New Jersey, which donated approximately 3,000 beef eyes in the course of this study, is gratefully acknowledged.

into the stroma of the cornea. A total volume of 0.75 ml. was distributed over 4 to 6 sites. The procedure was identical with that described by Herrmann and Hickmann[9,10] except for the larger amount of solution injected in our experiments. If necessary, solutions were neutralized and buffered to pH 7.0 with M/7 phosphate buffer. M/7 sodium chloride solution or, in some cases, M/7 phosphate buffer of pH 7.0 served as control solution, and whenever concentrations of an experimental agent less than M/10 were used, the dilutions were made with M/7 saline.

Following injection, the corneas were cut out, placed on watch glasses or, in order to maintain their natural shape, on inverted swimming cups, and incubated in a moist chamber at the temperatures and for periods of time specified. Following incubation of the corneas in the moist chamber, the corneal epithelium was removed by scraping with a scalpel, and tested for intercellular cohesion.

The two mechanical procedures and the criteria used for testing semiquantitatively intercellular cohesion on sheets of corneal epithelium were those described previously.[7] Histologic sections of experimental and control corneas were made after fixation in Zenker's solution and embedding in paraffin.

TABLE 1

EFFECTS OF METABOLIC POISONS AND OF SOME OTHER AGENTS ON INTERCELLULAR COHESION IN CORNEAL EPITHELIUM

Agents	Conditions (Standard Conditions: Incubation for 6–6½ hrs. at 38°C. and pH 7.0, unless otherwise specified)	Effect +: Loss of Cohesion −: No Loss of Cohesion	Concentration
Fluoride		+	M/35
	pH 4.4	−	M/14
	21–25°C.	−	M/7
Iodoacetate		+	M/200–M/100
	21–25°C.	−	M/50
Iodoacetamide		+	M/100
Arsenite		−	M/10
Fluoroacetate		−	appr. M/7
Ethyl Carbamate		−	M/10
Anaerobiosis		−	
Cyanide		−	M/10
Malonate		−	M/120
Atabrin		−	M/30
Azide		−	M/10
	pH 5.5	−	M/10
	pH 4.6	−	M/10
2,4-Dinitrophenol		+	M/100
	21–25°C.	−	M/20
4,6-Dinitrocresol		+	M/50
2,4-Dichlorophenol		−	M/10
Phenol		−	M/10
Gramicidin		−	Saturated
Methylol-Gramicidin		−	Saturated
Isoriboflavin		−	Saturated
Isoascorbinate		−	M/10
Heparin		−	1%
Pontocain		+	M/125
Cocain		+	M/70–M/60
	21–25°C.	−	M/60
Procain		−	M/55
Colchicine		−	6.5 mg. %
Histamine		−	M/20
Acetylcholine		−	M/10
Benzoquinone	4 hrs. 21–25°C.	+	M/50
Trinitrophenol (Picrate)	4 hrs. 21–25°C.	+	M/20

Results

The effects on intercellular cohesion produced by metabolic poisons and by some other agents* are summarized in Table 1 and are illustrated in Figures 1 to 10. The concentrations given in the table represent threshold concentrations in those cases where loss of cohesion was elicited with the subsequent mechanical procedures described previously. In some cases, examination of histologic sections revealed either minor or localized loss of tissue continuity with even lower concentrations of the agents. Those changes were seen following treatment with M/100 fluoride (fig. 7), M/1,000 dinitrophenol, and M/500 iodoacetamide. Fluoride,†

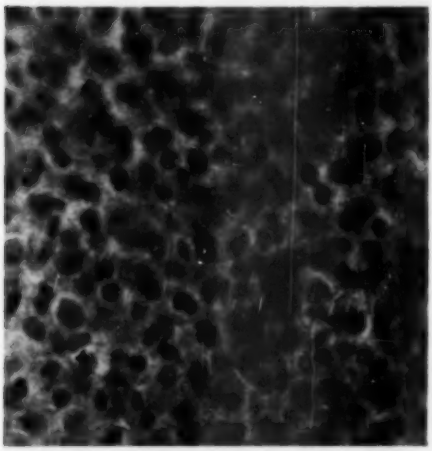

Fig. 1 (Buschke). Control. Sheet of beef corneal epithelium following injection of saline into stroma and incubation for 16 hours at 38°C. (×560). No loss of cohesion.

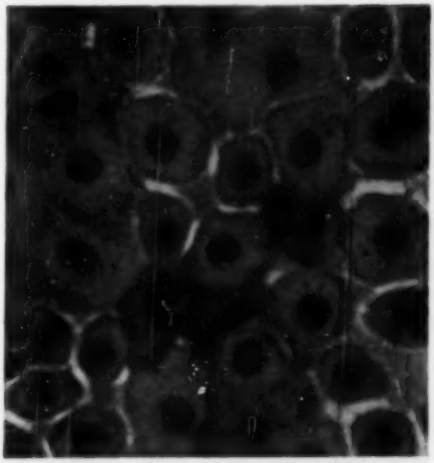

Fig. 2 (Buschke). Smear of beef corneal epithelium following injection of M/7 fluoride into stroma and six hours of incubation at 38°C. (×560). Loss of cohesion.

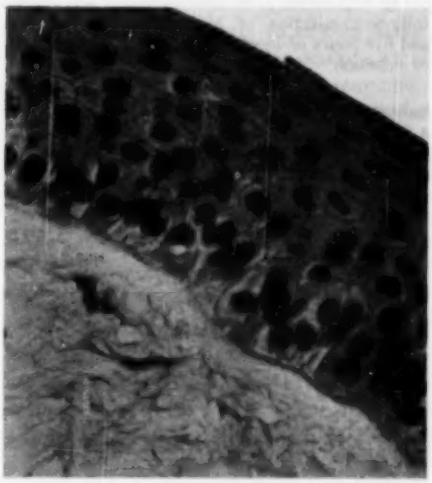

Fig. 3 (Buschke). Control. Paraffin section of beef cornea following injection of saline into stroma and six hours of incubation at 38°C. (×560). No loss of cohesion.

* Supply of the following substances used in this study is gratefully acknowledged: Fluoroacetate, from D. Glen Crabtree, Wildlife Research Laboratory, U. S. Department of the Interior, Denver, Colorado; Gramicidin and Methylol Gramicidin, from Wallerstein Laboratories, New York; Isoriboflavin, from Merck & Company Laboratories, Rahway, New Jersey.

† It is of interest that 1- to 2-percent sodium fluoride (that is, M/4 to M/2) had previously been used in histologic technique as a macerating agent for isolating cells of epidermis, lens fibers, and smooth muscle fibers.[11]

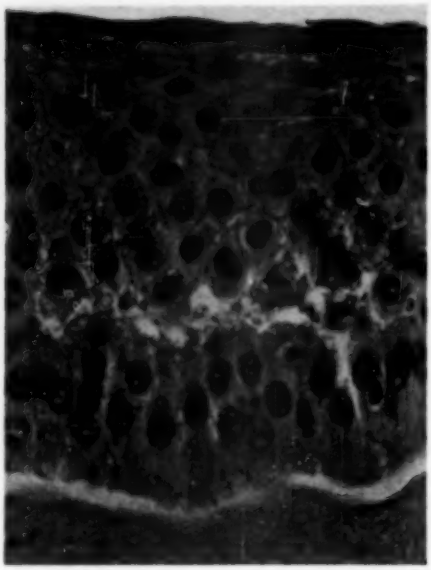

Fig. 4 (Buschke). Paraffin section of beef cornea following injection of M/7 fluoride into stroma and five hours of incubation at 38°C. (×560). Loss of cohesion.

iodoacetate, iodoacetamide, 2,4-dinitrophenol, 4,6-dinitrocresol, and some local anesthetics led to a marked decrease of cell cohesion after 6 to 6½ hours of incubation at 38°C. (figs. 1 to 6).

It is of interest that among the strongly effective agents, some are known as inhibitors of glycolytic pathways and some as inhibitors of phosphorylative processes.[12] Some other agents (quinone, trinitrophenol) produced a dissociation of the epithelial sheets into individual cells or cell groups with much shorter incubation times and at room temperature. These latter agents share the capacity to induce loss of cohesion at low temperatures and at shorter incubation periods with some detergents the effect of which on cell cohesion has been described in a previous report.[7] The differences in the kinetics of the effects between this group of agents on the one hand, and the metabolic poisons mentioned above on the other hand, are also illustrated in Figures 8 to 10.

It appears likely that quinone, trinitrophenol, and anionic detergents have a more direct effect, while, with some of the metabolic poisons and local anesthetics, obviously the continued presence of temperature-dependent processes is required to bring about eventual loss of cohesion. It is likely that these temperature-dependent processes, which persist in the presence of metabolic inhibitors, are proteolytic ones.

In this connection it is of interest to note that fluoride induces loss of cell cohesion at a pH of approximately 7.0, while it fails to do so if injected in an acetate buffer of pH 4.4; it is conceivable that the proteolytic enzymes in question have a pH optimum closer to neutrality.

In contrast to fluoride, iodoacetate, dinitrophenol, and so forth, no loss of cell cohesion was elicited, under otherwise identical experimental conditions, by cyanide, malonate, and anaerobiosis; that is, by agents which are known to interfere predominantly or primarily with respiratory processes. Furthermore, no loss of cohesion was elicited if corneas were incubated anaerobically for two

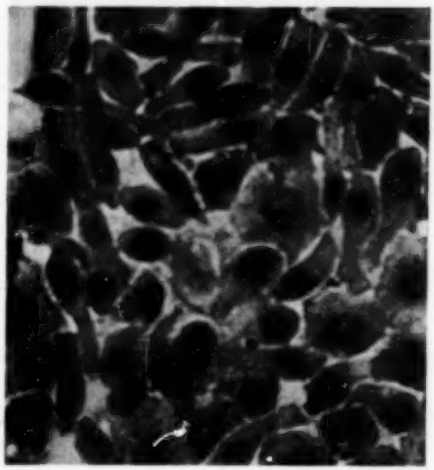

Fig. 5 (Buschke). Smear of beef corneal epithelium following injection into stroma of M/20 2,4-dinitrophenol and six hours of incubation at 38°C. (×560). Loss of cohesion.

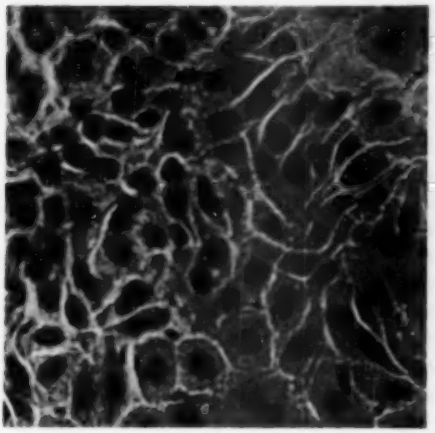

Fig. 6 (Buschke). Smear of beef corneal epithelium following injection of M/100 iodoacetamide into stroma and six hours of incubation at 38°C. (×560). Loss of cohesion.

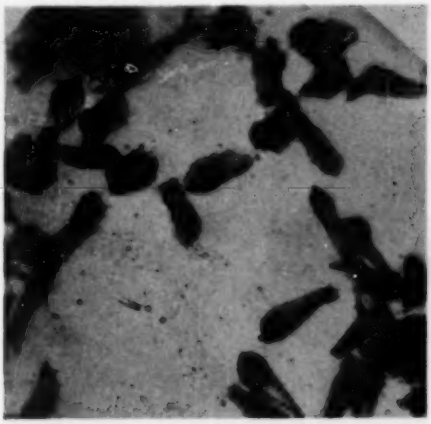

Fig. 8 (Buschke). Smear of beef corneal epithelium following injection of M/20 trinitrophenol into stroma and three hours of incubation at 25°C. (×560). Loss of cohesion.

hours, followed by aerobic incubation for six hours. Azide, which is known to interfere also with phosphorylative processes, had no effect.

Naturally, it will be necessary to accept with some reservations the absence of an effect on cohesion with these or any other agents listed in Table 1. Problems of diffusibility and of the possible production by these agents of secondary effects unfavorable to loss of cohesion may have to be considered.

Experiments with fluoride incubation under anaerobic conditions showed sometimes a less extensive dissociation of the epithelial

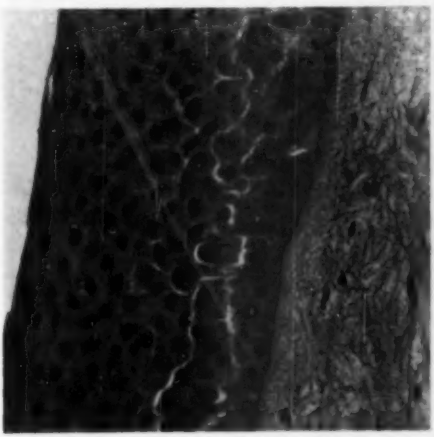

Fig. 7 (Buschke). Paraffin section of beef cornea following injection of M/110 fluoride into stroma and six hours of incubation at 38°C. (×560). Loss of cohesion.

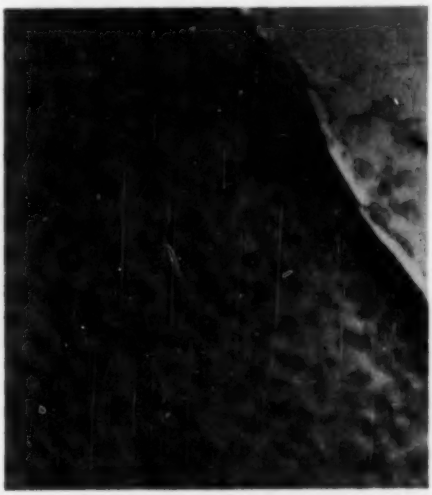

Fig. 9 (Buschke). Sheet of beef corneal epithelium following injection of M/20 2,4-dinitrophenol into stroma and five hours of incubation at 25°C. (×300). No loss of cohesion.

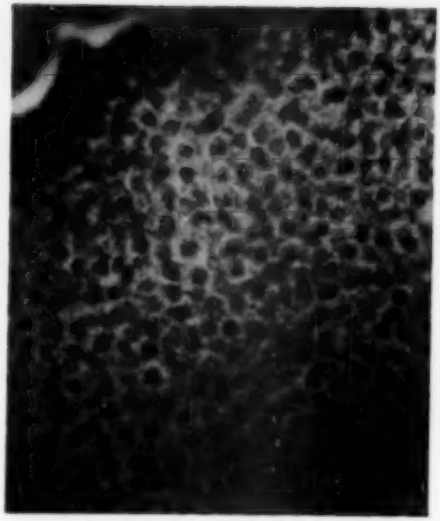

Fig. 10 (Buschke). Sheet of beef corneal epithelium following injection of M/7 fluoride into stroma and five hours of incubation at 25°C. (×300). No loss of cohesion.

sheet than was the case under aerobic conditions. However, anaerobiosis did not consistently and did not completely prevent the effects of fluoride and, therefore, the results of these latter experiments with anaerobiosis cannot, at present, be considered as significant.

As a sideline to these observations on cell cohesion, it may be mentioned that the qualitative integrity of one oxidative enzyme at least in the epithelial cells may be maintained even after complete isolation of the cells. Corneal epithelia isolated either with chymotrypsin or with M/7 fluoride give still a strongly positive indophenoloxidase reaction (fig. 11), indicative of the functional integrity of cytochrome oxidase.

Discussion

The observations reported here raise a number of questions in respect to both methods and interpretations.

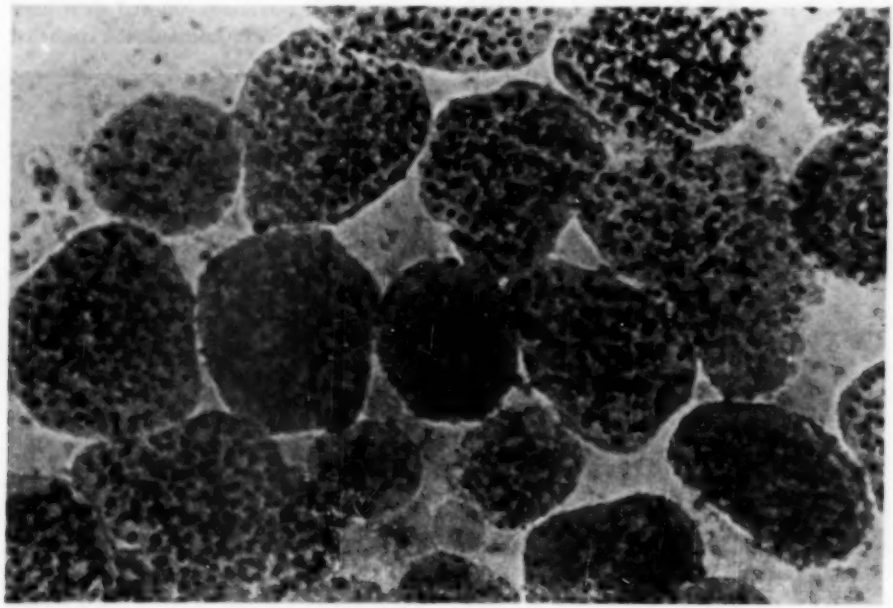

Fig. 11 (Buschke). Beef corneal epithelium cells isolated by incubation in 2.5 mg. percent chymotrypsin (×900). Positive indophenoloxidase reaction in the isolated cells.

1. Methods. In a previous paper, it has been pointed out already that all mechanical tests for tissue cohesion are, in effect, tests for "weak spots" in the tissue, and the results, therefore, indicate essentially the relative resistance or loss of resistance to mechanical stress of the intercellular regions, on the one hand, as compared with that of the cell bodies, on the other hand. This reservation has to be extended here, mutatis mutandis, to the observations on loss of tissue continuity in histologic sections following fixation and embedding of the tissue. In this case, the experimental agent or variable used prior to fixation may affect not only the properties of the intercellular regions, but may, for example, predispose the cytoplasm of the cell to shrinkage on fixation or dehydration thus imitating loss of intercellular cohesion.

2. Problems of specificity and site of action of metabolic inhibitors. Some of the quantitative data presented in Table 1 for threshold concentrations of metabolic inhibitors appear to be quite high in comparison with the generally known enzyme inhibiting concentrations of those substances in tissue sections, breis, or extracts in vitro. However, on examination of sections from fixed material, effective concentrations have been established for some of the inhibitors falling into the range of efficiency of those substances as metabolic inhibitors. The fact that the extent of tissue dissociation observed with these smaller concentrations was of a lesser degree, must not occasion any surprise.

It is well known from observations with other enzymes that residual activity of as little as 20 percent of the usually existing enzyme activity in the tissue may be sufficient for maintenance of function.[13] It would, then, not appear farfetched to assume that the application of inhibitors in metabolically effective concentrations (that is, in concentrations inhibiting enzyme activity by 80 to 90 percent) would lead one just to the threshold of recognizable effects on tissue organization.

At any rate, in our experiments with metabolic poisons, effective concentrations were of an order of magnitude to let these effects appear in a more specific relation to the cohesion mechanisms than similar effects produced by more drastic damaging procedures, such as freezing and thawing, or the injection of a saturated solution of butylalcohol or of 10M ethylalcohol with subsequent incubation at higher temperatures.

In a complex organized tissue like that of the cornea, it is difficult to relate the effects of any agent or variable directly and primarily to any special site in the tissue; that is, in our case to the intercellular regions or cell surfaces. It is conceivable that some of the agents which we found to affect cell cohesion exert their effects primarily on regions of the cell which are more or less remote from the cell surface. This possibility has to be considered as a serious one particularly because, in several cases and with concentrations inducing loss of cohesion, some changes in the degree of dispersity of the nuclear chromatin and vacuolar or granular changes in the cytoplasma were seen.

Finally, it must be considered as possible that some of the agents produce loss of cohesion by virtue of their affinities to certain tissue components independent from or in addition to their role as metabolic inhibitors. The well-known capacity of fluoride to form magnesium-fluoro-phosphate complexes[14] may not only lead to the inactivation of enolase, but may also make some structural proteins more susceptible to the effects of proteolytic enzymes due to withdrawal of magnesium.

In this connection, our previous observations[7] on the inhibiting effects of various earth alkali salts on loss of cohesion induced by proteolytic enzymes may be recalled. Similar considerations may be applicable to iodoacetate and dinitrophenol with reference to their capacities as sulfhydryl binding or oxidizing substances, respectively.

3. Relation of intercellular cohesion to adhesion between stroma and epithelium. In a previous report[7] some dissimilarities between intercellular cohesion and stroma epithelium

adhesion, as studied by Herrmann and Hickman,[9] have been pointed out. In the present study on intercellular cohesion, a congruence with the observations on adhesion of epithelium to stroma has been found both in respect to the positive results (loss of cohesion) obtained with fluoride and iodoacetate, and in respect to the negative ones (no loss of cohesion) obtained with anaerobiosis, cyanide, and malonate. The comments made in the preceding paragraphs may thus likewise be applicable to the corresponding observations on stroma epithelium adhesion, notwithstanding the obviously existing differences in the mechanisms of these two phenomena referred to previously.[7]

Summary

1. Loss of intercellular cohesion in corneal epithelium occurs on incubation of corneas for six hours at 38°C. with fluoride, iodoacetate, iodoacetamide, 2,4-dinitrophenol, 4,6-dinitrocresol, and some local anesthetics.

2. It is suggested that the loss of intercellular cohesion on incubation with these agents at higher temperatures is a manifestation of intrinsic proteolytic activity.

3. No loss of intercellular cohesion has been observed on similar incubation of the corneas with cyanide, malonate, azide, and several other agents in high concentrations, nor on incubation with anaerobiosis.

4. Quinone and trinitrophenol produced cell isolation with shorter incubation periods at room temperature.

5. The observations on intercellular cohesion reported here are discussed in respect to dosage levels, known metabolic effects of the applied agents, problems of specificity of effects, and in comparison with stroma epithelium adhesion.

210 East 64th Street (21).

The photomicrographs were made by Mr. Don Allen, Photographic Laboratory, Manhattan Eye, Ear, and Throat Hospital.

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Discussion

Dr. David Cogan (Boston): This paper by Dr. Buschke on proteolytic and metabolic poisons is obviously fundamental and aimed at finding out what the processes are which are involved. Perhaps it is premature to jump to any clinical applications, but one cannot help but look at his pictures and liken them to processes which one sees in histologic sections.

This freeing of cells and the free-floating cells that he had in some of his proteolytic studies are so much like the appearance in epithelial cysts that occur in the cornea when portions of the epithelium become trapped and the epithelium continues to grow within a cyst and casts off its cells. They look just like his diagrams, free-floating cells in the cyst.

One wonders whether proteolytic ferments within the cyst itself aren't responsible for that; and if so, why doesn't the proteolytic action keep on going? Why is it that apparently it just frees the surface cells? Why doesn't it continue to cause a lot of disruption of the deeper layers? It would be interesting to know what Dr. Buschke says about that, although obviously that is a very uncontrolled observation as compared with his.

Another clinical application that occurs to one hearing Dr. Buschke in his presentation is this loss of adhesion between the epithelium and the stroma which Herrmann has observed particularly with butyl alcohol.

Several years ago Dr. Grant and I had occasion to study an epidemic of butyl alcohol poisoning in girls who were employed in a rubber factory where they were using butyl alcohol as a solvent. The characteristic of the corneal lesion was the occurrence of vacuoles. We never had the courage nor the occasion to remove the epithelium; because of the similarity to relapsing keratitis in the vacuoles and also in the symptoms, we inferred that the characteristic abnormality was a loosening of the epithelium.

Dr. Jonas S. Friedenwald (Baltimore): I think this is a very important piece of work, and I am going to ask only one brief question.

Dr. Buschke suggests that the mode of action of several of the metabolic inhibitors which led to separation of the epithelial cells is via an activation of proteolytic enzymes. In his own previous studies he found that the effect of proteolytic enzymes was diminished by the presence of calcium and other bivalent cations, and I wonder whether he has any data in regard to these present agents. Of course fluoride would be a difficult one to tell about, but iodoacetate might give quite critical results.

Dr. Zacharias Dische (New York): I would like to ask Dr. Buschke how he calculates his concentrations. If I understood him, the solutions were injected into the stroma of the cornea. It is difficult to get the right idea of what his real concentration was. I suppose it was a concentration of the solutions that was injected.

Under these conditions it is most important to know the ratio between the volume which was injected and the volume of the cornea, because many of these concentrations, as far as the effective substances are concerned, are just the limit of their characteristic metabolic effectiveness. For example, fluoride, M/200, is just about the concentration at which you get a real inhibition of the glycolysis.

On the other hand, iodoacetate in concentration of M/200 is no more selective in so far as glycolysis is concerned, and at the concentration of M/10 of cyanide, glycolysis is inhibited to a very considerable extent. As far as fluoride is concerned, I think Dr. Friedenwald made the point that it could work by precipitating calcium, and as the calcium itself probably has a considerable influence on the adhesion, this may be the mechanism of the effect of fluoride rather than its influence on the metabolism.

DR. WILLIAM BUSCHKE: I was very much interested in Dr. Cogan's comments. I have nothing definitely convincing to say about what stops the process of proteolysis in the formation of bullae which are apparently connected with some autolytic processes.

It is possible to speculate about it, that if a proteolytic process has been going on in some limited region of the tissue, the breakdown products may represent a self-limiting effect, or that possibly in the surrounding normal tissue some inhibitor substances are available which have an inhibiting effect on the progress of the lesion.

In regard to Dr. Friedenwald's question about the effect of iodoacetate and its relation to calcium. I would like to ascertain a little more what precisely was meant in regard to the relation to the calcium.

DR. FRIEDENWALD: I may have misunderstood what you said, Doctor, but I understood you to imply that these metabolic inhibitors might not produce this effect directly by an inhibition of phosphorylation but by a stimulation of proteolysis. You said that specifically in relation to fluoride, and implied that it might also be true in regard to iodoacetate; if so, then in view of the previous work, one might be able to establish that fact or contradict it by tests with calcium.

DR. BUSCHKE (closing): If I understand you correctly, it would mean to apply simultaneously calcium to see if the effect of iodoacetate would be abolished. I think this would be a very interesting experiment; I haven't done it yet.

In regard to Dr. Dische's question about the problem of concentrations: The amount of solution injected into the cornea was 0.75 ml., which is higher than had been used in the experiments of Herrmann and Hickman. A beef cornea weighs approximately 500 mg.; so that would represent a dilution factor of about 40 percent. In addition, by weighing the corneas prior to and after the injection, it was found that only approximately 60 percent of the solution remained in the cornea; approximately 40 percent escaped through the canal of injection; that was very similar to the experience of Herrmann.

Therefore, I think it would be fair to assume that altogether a dilution factor of about 3 to 4 for the final concentration in the stroma would be right. How much of it really appears in the epithelium, I don't know, but I think that brings the concentration for some of the agents into the region of metabolic inhibitors, even for the test with the shearing method.

I showed you, however, a picture of a paraffin section from a cornea which had been treated with M/100 fluoride, in which the epithelium showed some loss of tissue continuity; similar results on tissue continuity were seen in paraffin sections following incubation of corneas with M/1,000 dinitrophenol and with M/500 iodoacetamide.

I wonder if these figures are not well within the range of metabolic inhibitions. Still, I have no proof that these effects are due to specific inhibitory effects on glycolysis or phosphorylative activities in the tissue, or whether they would be due to some independent effect on some susceptible groups in the tissue or perhaps in some cases to calcium-binding.

CHOROIDITIS PROLIFERANS*

The Charles H. May Lecture

Adalbert Fuchs, M.D.
New York

I beg to express my sincerest thanks for the invitation to give the Charles May lecture. This is a great honor for me and I appreciate it especially because Dr. Charles May was a very good friend of mine. He was a great scientist and scholar, with profound knowledge and a special gift for teaching. His textbook with its many editions is the best proof of this. He had such a fine character and a warm heart and spoiled me with kindness when I was in New York 24 years ago. I was deeply touched when I got the news that he had passed away.

I have chosen as the subject of this lecture Choroiditis proliferans, first because I believe that this new type of fundus disease may interest you and second because this disease is more frequent than is generally assumed.

I observed my first case many years ago and described it in my book *Die Erkrankungen des Augenhintergrundes* on page 135 (1943).

A 16-year-old boy from Albania had hereditary syphilis. Three years previously his vision had become worse in both eyes and, when I saw him, he could count fingers only at a few meters. His visual field was restricted in all directions. The Wassermann reaction was positive and did not change after energetic treatment.

Both papillas were somewhat pale, the retinal vessels narrow. At both posterior poles there were broad, sharply outlined, intense whitish strands of connective tissue, which were curved and ended in a flamelike or ragged shape (fig. 1). These strands partly surrounded the papilla; they were interlaced and crossed by the retinal vessels. At the posterior poles, the fundus did not show many changes except that above the papilla there was a broad, yellowish, sharply outlined area, leading somewhat upward. At the periphery there were some small choroidal foci and numerous small pigmented dots.

I considered that these whitish bands were caused by connective tissue which was formed after a subretinal hemorrhage or after an inflammatory exudate. Therefore, I considered this fundus change a sequela of a choroiditis exudativa or a Harada's disease.

Fig. 1 (Fuchs). A case of choroiditis proliferans, showing the whitish strands of connective tissue which curved and ended in a flamelike shape. (Republished with permission from: Fuchs, *Die Erkrankungen des Augenhintergrundes.*)

I did not see a similar disease for many years after this first case. One can find somewhat similar stripes of whitish color behind the retina once in a while in other fundus diseases. For instance, in a case of reattachment of a serous ablatio retinae, isolated, thin, whitish bands of connective tissue can be found amid other fundus changes.

Figure 2 shows the fundus of a woman, 20 years of age, who had had retinal detachment six years previously. The retina re-

* Presented before the Section on Ophthalmology, New York Academy of Medicine, May 17, 1948.

turned spontaneously to its original position and she could count fingers at 1.5 m. Amid very considerable displacement of pigment one could now see in the area where the retina was formerly detached and later on became reattached, a small number of whit-

Fig. 2 (Fuchs). Reattached retina, showing some kind of connective-tissue strands or filaments between choroid and retina. (Republished with permission from: Fuchs, *Die Erkrankungen des Augenhintergrundes.*)

ish, partly bifurcated, exceedingly narrow stripes, which were partly pigmented and were crossed by the retinal vessels. These fine stripes or lines represented, without doubt, some kind of connective-tissue strands or filaments between choroid and retina.

There also has been reported a combination of choroiditis proliferans and retinitis proliferans. A woman, 34 years of age, had had an impairment of vision for many years in the left eye. She could count fingers at 1.5 m.; of the visual field only a part remained on the temporal side. The general examination was completely negative. The case represents Hippel's disease. The daughter of this patient had a similar disease and later on developed a hemangioma of the spinal cord and died.

The papilla was indistinct and yellowish (fig. 3). Three of the retinal vessels showed gigantism and were tortuous. There was a hemangioma at one side of the nasal vessel. The retinal vessels were partly covered by connective-tissue strands and plates which looked white like tendons. Apparently some of this connective tissue was also lying on the outside of the retina, as we could see by the whitish discoloration of those parts where the retina was only detached to a minor degree. Besides these irregular whitish membranes, we also found numerous, very thin whitish strands; these had a special tendency to have a straight course, to divide and bifurcate; and they showed, now and then, small knot-shaped enlargements. I shall speak later about these straight filaments and the whitish connective-tissue plates which cover larger areas.

Fig. 3 (Fuchs). Combination of retinitis proliferans and choroiditis proliferans in Hippel's disease. (Republished with permission from: Fuchs, *Die Erkrankungen des Augenhintergrundes.*)

Chinese case reports

In China, I saw a number of cases of choroiditis proliferans. I was able to get paintings of some of these cases and I will give a brief history of them:

Case 1. A soldier, aged 51 years, was injured some years ago by a gunshot which passed just in front of his eyes without leaving any scars on the face. At first he could see nothing with the right eye, but later on he could see hand movement. The fundus was only tesselated on the nasal part; the temporal part of the fundus beyond the papilla was stained partly brownish, partly dirty reddish (fig. 4). The papilla was normal.

In the extreme central periphery was a large, whitish, atrophic focus surrounded by an irregular, pigmented band. Behind this focus three bizarre pigmented foci were situated. At the posterior pole some whitish, distorted, partly branched connective-tissue strands were situated. They were crossed by the retinal vessels and ran partly from the papilla

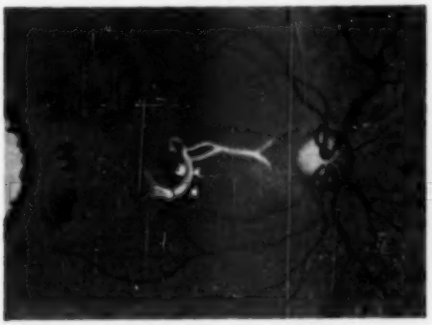

Fig. 4 (Fuchs). Choroiditis proliferans following a gunshot wound.

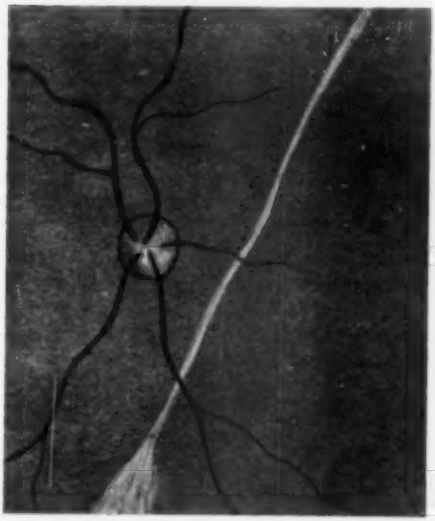

Fig. 5 (Fuchs). Choroiditis proliferans following reattachment of a retinal detachment.

to the macula where the majority of these strands were localized.

Case 2. A young man had a retinal detachment in the left eye some years ago and had been operated upon. Vision was counting fingers. The fundus showed the same color everywhere; an obliquely running whitish stripe of connective tissue was conspicuous (fig. 5.) It ran from the temporal upper quadrant downward to the nasal side. This stripe was quite straight, of equal breadth, and split up below like a fan at the periphery. The retinal vessels crossed this stripe.

Fig. 6 (Fuchs). A case of choroiditis proliferans which followed reattachment of a retinal detachment (right eye).

Fig. 7 (Fuchs). A case of choroiditis proliferans which followed reattachment of a retinal detachment (left eye).

Case 3. A man, aged 27 years, said that his vision was considerably impaired 10 years ago and that there was a shadow in front of his right eye. Three years later the vision of this right eye became worse and a Japanese oculist diagnosed a retinal detachment. At that time the left eye was normal, but later on the vision became worse and three years ago a detachment of the retina was diagnosed in both eyes.

The Wassermann reaction was negative; general

examination showed no special symptoms. It was not possible to get any information as to the general symptoms of Harada's disease. Vision in the right eye was hand movements above only. Of the visual field only a small part, temporal and above, remained. Vision of the left eye was 1/60; visual field for hand movement normal.

In both eyes dust-shaped vitreous opacities were present. Both papillas were normal in color and sharply outlined (figs. 6 and 7). The fundus was of an equal grayish-red without any atrophy of the pigment epithelium. Both eyes showed a very similar fundus picture, consisting of slightly curved, partly branched, whitish stripes beneath the retinal vessels. In some places there were knot-shaped enlargements of these bands. In the left eye an extensive membrane of whitish color was situated in the macular region. This membrane had a ragged outline on the temporal side where this membrane gradually disappeared.[1]

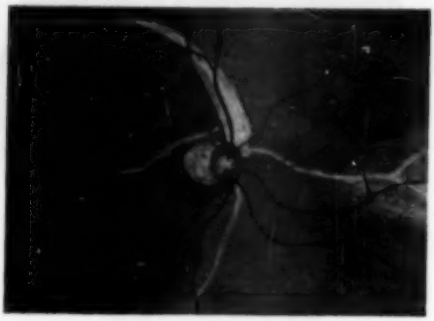

Fig. 8 (Fuchs). Choroiditis proliferans.

Comment

One cannot say with certainty that this case was Harada's disease. It is exceedingly difficult to get an adequate history of a case in China and so it was not possible to find out whether the general symptoms of Harada's disease had occurred. The binocular detachment, which very soon disappeared, and the fine opacities of the vitreous certainly would suggest a sequela of Harada's disease.

Case 4. A boy, aged 19 years, had a visual disturbance of the right eye, four years ago. He had had no pain in the eye or in the head and no general symptoms. General examination and the Wassermann reaction were negative. He had, when examined, no precipitates and no traces of posterior synechias. He could count fingers at two meters. The visual field was not restricted for hand movements.

The papilla was normal and showed a broad myopic conus on the temporal side (fig. 8). The temporal half of the fundus was markedly tesselated while the nasal half showed a whitish gray color which was separated from the tesselated part by a rather sharp line. Broad strands of connective tissue ran from the papilla in all four directions. The broadest stripe led upward and separated the tesselated fundus from the whitish gray fundus; it ran far to the periphery and was lying, like the other strands, beneath the retinal vessels. A narrow stripe, distinctly radiated like the others, ran to the nasal side, there bifurcated.

There was one area where the fundus had an intensively white color which made it stand out from the remaining whitish part of the fundus. A third stripe of equal breadth ran downward, and a fourth stripe started from the broad strand which led upward and ran above the temporal conus of the papilla as a fine stripe toward the macular region.

Comment

Without doubt, the whole fundus was originally tesselated. Later the nasal part of the fundus changed color due to a thin layer (probably connective tissue) covering the choroid and strongly reflecting the light. We have no proof that originally Harada's disease had been present, but I believe that this case, just as did the next case, showed a special forme fruste; that is, an incomplete type of Harada's disease which did not show all the symptoms, especially the general ones. That such cases exist we know from reports of cases in which the eye symptoms were slight but were combined with very striking and severe general symptoms; for instance, loss or bleaching of the hair, eyelashes, and eyebrows, meningial symptoms, and vitiligo.

Harada's disease is a kind of virus affection which sometimes shows very slight symptoms and sometimes very severe symptoms that lead to Vogt-Koyanagi's disease. When this occurs, the iritis with its infiltrations and pupillary membrane are striking and hide the changes in the fundus. Some cases are very mild in the beginning but become exceedingly severe after weeks or months and lead to blindness; other cases are very alarming even in the first stage.

Case 5. This case was similar to Case 4 except that the course was milder. A boy, aged 18 years, had had retinal detachment of the left upper and nasal quadrant and was treated in the E.E.N.T. Hospital in Chengtu. His vision was 6/30. General symptoms had not been observed; Wassermann test was negative. After a month of bed rest, the retina became reattached. His vision improved and white stripes were seen in the fundus. No symptoms of iritis were mentioned. The vision was +1, 6/10.

The papilla and the visual field for white were normal; the fundus tesselated. On the temporal side there was a whitish discoloration in the lower temporal region and the white color became especially conspicuous and shaggy (fig. 9). Two slightly wavy white stripes ran from the upper temporal to the lower nasal side. They were divided at both ends into several branches and showed button-shaped enlargements. These enlargements were sometimes situated at the place of the bifurcation.

The central parts of these two stripes were in the tesselated fundus. The vessels of the retina ran over these stripes and the whitish area without any irregularity. The visual field for white was contracted only slightly, while the field for red was lacking in the superior half and normal in the lower half.[8]

The whitish temporal half of the fundus had a higher refraction (of one diopter in parts) than the other fundus. There was a question as to whether or not a minimal detachment of the retina was present. I came to the conclusion that there was no detachment, especially because the visual field for red which corresponds to this area was present; in this area certainly there would be no sensation for red if there had been a minimal separation between retina and pigment epithelium. It is noteworthy that, just at the site of the original detachment, the field for white and red was intact. Certaintly one could not determine why only the upper half of the red visual field was absent.

Comment

I considered this case, like the three preceding ones, to show a forme fruste of Harada's disease. In all four cases there was no evidence of general symptoms, and no signs of iritis were present. Only in Case 3 had we found dustlike vitreous opacities. It would seem that, perhaps, we are not justified in considering these cases of Harada's disease.

On the other hand, we have here a number of

Fig. 9 (Fuchs). Choroiditis proliferans after retinal detachment. Vision was +1, 6/10.

Fig. 10 (Fuchs). Pigmented choroiditis proliferans following Harada's and Vogt-Koyanagi's disease.

reattached retinal detachments in which we are unable to find a sharp outline (fig. 2) between the area of former detachment and the rest of the fundus; perhaps because of the brief duration of the detachment. Furthermore, we have in the cases herein reported a type of connective-tissue formation which is apparently exceedingly unusual. As the cases of Harada's disease are not rare in China and are sometimes very mild, I believe that one is entitled to accept these cases as showing the sequelae of mild cases of Harada's disease.

Case 6. A sixth case which belongs in this group is of special interest. A Chinese woman, aged 45 years, had had, for some time, shallow anterior chambers and thickened and infiltrated irides (the irides gave the impression of an iris bombé). There were numerous posterior synechias, but no seclusion of the pupils. Many precipitates and vitreous opacities were present.

Four months previously the fundus was not visible but two months later one was able to see the blurred papilla. One month later the woman lost her hair and the eyelashes became white. When examined, the tension was normal in the right eye and slightly elevated in the left. Vision was 6/36 in both eyes, and the upper part of the visual field was absent on both sides.

The fundus of the right eye showed a reddish, blurred papilla which was surrounded by a pinkish band (fig. 10). The whole fundus was covered by small and larger indistinct spots which were partly yellowish-red, partly pigmented. There was a conspicuous formation of connective tissue beneath the retina, partly whitish, partly grayish. A broad whitish striated band ran from the papilla upward and a similar irregular, sharply outlined mass was found beneath the papilla. All these membranes lay beneath the retinal vessels.

In addition, there were a number of irregular, slightly grayish spots which showed, partly by their fine, long extensions, that they represented pigmented connective tissue. A spindle-shaped for-

mation on the temporal side showed clearly a whitish center; another part was connected with a whitish connective-tissue mass below.

The left eye had a very similar fundus with small and large whitish pigmented spots. A larger focus was situated below lying beneath the retina and showing a grayish extension leading upward, while the whole mass had a whitish center and showed a more grayish border[3] (fig. 11).

Comment

Without doubt we have here a case which shows a transition from Harada's disease to Vogt-Koya-

Fig. 11 (Fuchs). Pigmented choroiditis proliferans following Harada's and Vogt-Koyanagi's disease.

nagi. The general symptoms and the heavily infiltrated iris together with precipitates and vitreous opacities indicate quite clearly the diagnosis of Vogt-Koyanagi's disease. At the time, since the fundus could not be seen, apparently a retinal detachment was present. A combination of iritis and retinal detachment form the picture of Harada's disease. Since the participation of the iris in this case was so severe, we can assume that it was a transitional case which combined the symptoms of both diseases, Harada's and Vogt-Koyanagi's.

This case is also interesting because a large part of the connective-tissue formation between choroid and retina became pigmented.

Discussion

I have reported six cases seen in China which belong to the type choroiditis proliferans. They showed two characteristic changes: (1) Slightly tortuous or straight strands of connective tissue lying beneath the retinal vessels, frequently branching and often showing knot-shaped enlargements; (2) often large areas of white color where the choroid was obscured. Apparently some cases were caused by inflammatory detachment of the retina (Harada's disease). Cases 3 and 6 would seem to show abundant evidence to support this claim.

The histopathologic structure of these whitish stripes and coatings could not be determined because there was no material for microscopic examination. I imagine, however, that the long, thin, and sometimes branched strands were originally fibrinous filaments which were formed in the albuminous fluid of the retinal detachment. The whitish areas of the fundus, which had the clinical appearance of connective tissue, originate, according to my opinion, from sedimentation of albumin which later becomes denser and organized. We have observed such sedimentation in an anterior chamber where, later on, a whitish opacity could be seen outlining the posterior wall of the lower part of the cornea.

My theory of the anatomic structure of the changes in choroiditis proliferans is supported by the study of a slide I had the opportunity to examine in China.[4]

A metastatic carcinoma of the choroid is present, having the characteristics of a scirrhus and we can recognize (fig. 12) abundant proliferation of connective tissue (C.T.) in the choroid, enveloping the carcinoma metastasis (Ca). The pigment epithelium (Pi) is lacterated, probably due to shrinkage during fixation, and is very irregular. Its cells are mostly destroyed and the layer of the pigment epithelium is more or less replaced by lacerated pigment deposits. This shows that apparently considerable inflammation was present, which had led to the destruction of the cells.

The remains of pigment epithelium are covered by a fine layer (L) of connective tissue which extends over a large area in equal amount. Over this layer there is a large artificial slit in communication with the slits in the albuminous fluid. This large slit is partly filled with detached and floating cells (P) of the pigment epithelium.

The upper part of Figure 12 shows the coagulated albuminous subretinal fluid (S.F.) which is broken into pieces. This fluid extends to the retina but the latter is not visible in the picture. In the big slit, we find near (St) a cross section of a connective-tissue strand showing a more or less homogeneous tissue in the center with some cross sections of nuclei of connective-tissue cells; this strand is surrounded by a fine sheath formed by connective-tissue cells.

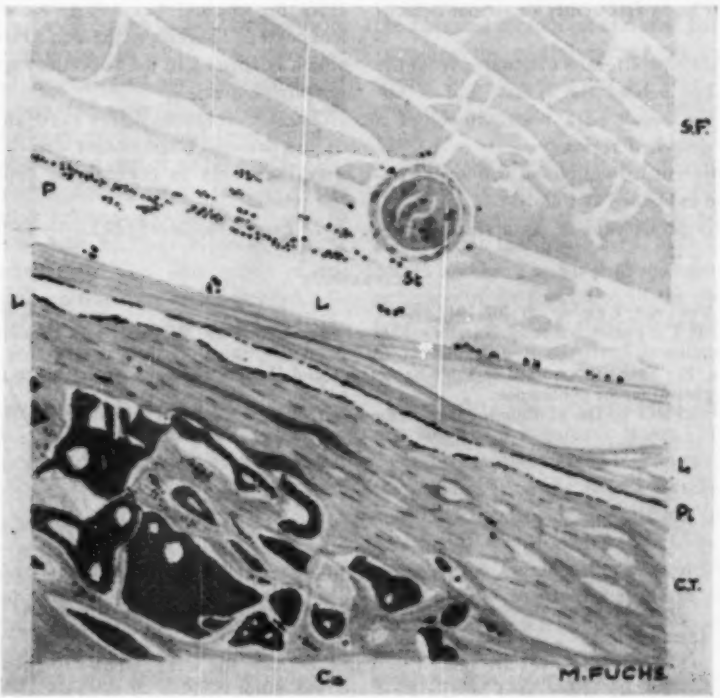

Fig. 12 (Fuchs). Metastatic carcinoma of the choroid with a layer of connective tissue on the choroid (L) and a filament in the subretinal space (St).

Without doubt there was an inflammatory fluid between the retina and the carcinomatous choroid. The signs of the inflammation can be recognized by the destruction of the pigment epithelium, by the loose, deteriorated and floating pigment-epithelium cells, by the red color of the subretinal fluid which shows a high content of albumin, and finally by the formation of the connective tissue. These newly formed elements of connective tissue are very similar to choroiditis proliferans.

There are both a fine layer of connective tissue upon the choroid (L) and connective tissue filaments (St). The latter probably were originally fibrin in the fluid and would have been pressed against the retina if the retina had been reattached. Probably we have the same anatomic explanation for white stripes in Hippel's disease, which I mentioned before, and also in choroiditis proliferans, although I am unable to prove it.

The name, choroiditis proliferans, is a

morphologic term and is an analogy of retinitis proliferans. It means formation of connective tissue after an inflammation of a certain membrane. In both types different causes can produce the same clinical picture. The difference between choroiditis proliferans and retinitis proliferans is that the latter is established on the inner surface of the retina and leads frequently to retinal detachment.

Choroiditis proliferans originates from the choroid, lies behind the retina, and is apparently the result of a reattachment of a formerly detached retina.

The different formations of connective tissue can be explained as follows:

Retinitis proliferans is, as a rule, the result of a severe inflammation which shows a real exudate with cells such as are seen in cases of metastatic ophthalmia and repeated hemorrhages of the vitreous or after injuries.

The connective-tissue formation due to detachment of the retina is the effect of much milder inflammation producing only a fluid rich in albumin, and probably some fibrin from the choroid but not an exudate with leukocytes. Therefore, the connective tissue which is formed in the subretinal space does not shrink much.

These membranes do not cause an increase of the present inflammatory detachment but may later help to connect the choroid and the retina.

18 East 77th Street (21).

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2. Tang, P. C.: Forme fruste of Harada's disease. Submitted to the World Health Organization for publication.
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4. I am indebted to Dr. E. Cunningham of the West China Union University for this specimen.

Ophthalmic Miniature

Jean Mery made the first observation through the pupil of the ocular fundus.

"When cats' eyes are placed in water, because the irregularities of the cornea are obliterated by the fluid and the pupil dilates, all the rays of the sun that fall on the transparent cornea pass through it and enter into the eyeballs illuminating them so strongly that one can then very distinctly see the end of the optic nerve and the choroid with all of its colors and its vessels."

Communication to the Royal Academy of Sciences, Paris, November 12, 1704.

Des mouvements de l'iris et par occasion de la partie principale de la vue.

CRANIOFACIAL DYSOSTOSIS (CROUZON'S DISEASE)

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Washington, D.C.

Craniofacial dysostosis is a syndrome of craniofacial deformity resulting from premature synostosis of the sutures of the base of the skull and of the face. This syndrome was originally described in 1912 by Crouzon, a Paris physician. In 1937, Atkinson[8] reviewed all the cases of this syndrome that had been reported since 1912, a total of 86 cases. Of this number, 15 had been reported by Crouzon over a period of 20 years.

Craniofacial dysostosis is one of many very similar entities which are difficult to dissociate because of their blending clinical and pathologic findings. This group of entities make up the craniostenoses.[7] Oxycephaly is one of the more prominent entities of this group and, no doubt because of its close association with Crouzon's disease, many cases of the latter have been called oxycephaly.[9] All craniostenoses have in common premature synostosis of some of the sutures of the skull.

THEORIES OF CAUSE

To be anything but speculative about the etiology of this syndrome is impossible because so little is known of the details in the embryologic development of the membranous skull. Crouzon and Regnault, writing in 1929, felt that an inflammation occurred around the sutures causing premature synostosis and subsequent arrest of growth.

Ida Mann,[10] in discussing the etiology of oxycephaly, pointed out that fetal rickets, syphilis, fetal meningitis, and osteitis from metastatic infections in utero have little significance in the etiology of this skeletal deformity. She classifies it as a true developmental anomaly of germinal origin and places the fundamental defect in the mesoderm which goes to make up the bones of the base and sides of the skull.

The mesoderm involved in the formation of the base and sides of the skull of man is from two sources; the paraxial and the visceral mesoderm.[10-13] That mesoderm lying along the body axis arranged in myotomes is the paraxial mesoderm and that portion surrounding the rostral end of the ectodermal neural tube becomes the paraxial mesodermal contribution in the formation of the skull.

The visceral mesoderm, which is only found in the head region, lies ventral and outside the paraxial mesoderm, and is derived from the five-paired branchial (visceral) arches. The visceral mesodermal contribution in the formation of the skull comes from the paired maxillary processes which bud from the first-paired branchial arches (mandibular arches).

From the maxillary processes develop the maxillary and zygomatic bones. The paired palatine processes extending inward toward the midline from the paired maxillary processes fuse in the midline to form the palate. The maxillary processes also form visceral mesodermal condensations ventrally, surrounding the paraxial mesoderm which ultimately develops into the alisphenoids, pterygoids, and temporals. The body of the sphenoid and remaining bones of the skull are of paraxial mesodermal derivation.

Low in the phylogenetic scale, as in the case of reptiles and fishes, the brain is narrow, consequently there is no need for a large skull. In these species the skull is formed by condensations of the paraxial mesoderm with no contribution from the visceral mesoderm. Higher in the phylogenetic scale the brain increases in width, consequently the skull is larger and the visceral mesoderm contributes to the formation of the skull. Ida Mann[10] cannot resist speculating that in oxycephaly occurring in the human skull, there exists a possibly atavistic

arrest of that portion of the skull derived from the visceral mesoderm of the maxillary processes.

Park and Powers[8] have pointed out that the defect is in the germ plasm which manifests itself by premature synostosis. They feel that the site of the congenital defect is the interstitial mesenchyme which normally separates the skull bones in their suture lines.

Pathology

If Ida Mann's contention is correct, then those structures which develop from the maxillary processes would be affected, that is, zygomatic, maxillae, palantine, alisphenoid, pterygoid, and temporal bones. According to Park and Powers[8] the defective interstitial mesenchyme of the involved suture lines fails to produce new bone growth, which tends to produce early calcification of the suture line.

The premature synostosis eventually results in a skull which is unable by normal growth stimuli to increase in capacity sufficiently to accommodate a normal and rapidly growing young brain. The intracranial pressure consequently is increased, but compensation of the intracranial tension may be attained by the following means.

The thin skull bones may bulge forming a boss, the nonsynostosed sutures may be separated forming dehiscences, or a compensatory overgrowth may occur along the nonsynostosed sutures increasing the measurement of the skull in a direction perpendicular to the nonsynostosed sutures. Frequently the anterior fontanelle is found to remain beyond the first year of age with pulsating intracranial contents bulging into it.

The intracranial pressure depresses the fossae, especially the middle and posterior fossae, increasing the vertical diameter of the cranial vault. Cerebriform convolutional markings are eroded on the inner table of the skull by the elevated pressure. Because the weakest region of the base of the skull is the sella turcica, this area may be enlarged in all its measurements by the increased pressure with no erosion of any of its parts.[6]

In the event that the intracranial hypertension is not adequately compensated by secondary bony changes of the skull, signs of decompensation appear. Papilledema or secondary optic atrophy is a reliable sign of decompensated intracranial hypertension. However, not all writers are in accord as to the etiology of the optic atrophy, yet the majority feel that the secondary optic atrophy is the sequel to a previous papilledema.[1-2, 5, 7-8, 10]

Krause and Buchanan[5] state that the optic atrophy can be the result of intracranial hypertension, or mechanical traction of the nerves due to lengthening of the optic canal, or constriction of the nerves by the narrowed optic foramina. Behr[14] concludes from an anatomic study of four cases of oxycephaly that there is a shift of the roof of the optic canal backward over its floor, and that the carotid artery passing under this posterior projection of the canal roof compresses the nerve.

Ida Mann[10] feels that the optic atrophy of oxycephaly is either secondary to papilledema, or due to a kinking of the optic nerve at the optic foramen as its exits from an abnormally downward directed optic canal and courses sharply upward to follow the abnormally upward slope of the distorted orbit. Rubin[8] remarks that the cases of unilateral optic atrophy are not explained by increased intracranial pressure.

The premature synostosis of the zygomatic, maxilla, alisphenoid, temporal, pterygoid and palatine bones results in a hypoplasia of the bones of the face and orbit, a high arching of the palate, and locks the orbits in the widely separated, laterally directed fetal position (hypertelorism).[10] Expanding intracranial hypertension depresses the roof of the orbit so that it slopes abnormally downward posteriorly, thereby being more vertical than normal. The peculiarly shaped and hypoplastic orbit forces the nor-

mal orbital contents forward, creating a conspicuous exophthalmos, which Atkinson[5] reports existed in all 86 cases that he reviewed.

The skull is the only portion of the skeletal system involved in the premature synostosis, although bilateral, symmetrical syndactylism of the upper extremities has been recorded[1, 5] as an associated finding.

Clinical course

The hereditary nature of this syndrome has been widely discussed. In fact, Crouzon considered it to be one of the essential characteristics of the syndrome and the first cases he described occurred in a mother and son. Atkinson[5] reported that in 28 of the 86 cases he reviewed there was no familial or hereditary history. There is no racial or sexual predilection.[5]

The distinctive craniofacial deformity is conspicuous at birth. This includes exophthalmos, hypertelorism, and frequently an associated divergent strabismus. The upper face is broad, having a recessed appearance, and the palate is highly arched.

Since the head grows rapidly during the first few months of infancy, it is usually within this period that the peculiar shape of the skull becomes manifest.[2] There may develop a scaphocephaly or acrocephaly, and/or the skull may have frontal, parietal, or occipital bosselations. The vertical diameter of the skull usually becomes increased and the ears are tipped posteriorly and pulled inferiorly to a lower plane than normal.

Although the nasal bones are normal, the nose appears prominent when hooked to the hypoplastic maxillas. The septum is often deviated and the breathing stertorous. The mandible is normal and, at an age when the mandible has sufficiently developed, attention is easily directed to the relative prognathism. When the teeth erupt they are malocculded.

X-ray films will reveal cerebriform or digiform markings on the thin skull bones and the sella turcica may be enlarged in all diameters with no destruction of its parts.[4, 6, 8] The maxillary sinuses are rudimentary or absent.[6]

A decompensated increased intracranial pressure may be present at birth or may develop subsequently at any time prior to cessation of the growth of the brain.[7] A sustained decompensated intracranial hypertension may provoke headaches, convulsions, or result in mental and visual impairment.

Prognosis

The rate of brain growth is very rapid during the first year and progressively decreases until adult size is attained by the eighth year. Therefore, if the intracranial tension can remain compensated until the age of eight years, the prognosis is excellent for a normal vision and mental state for the remainder of life. Because the mechanism for compensation of the intracranial hypertension involves skeletal changes in the skull, Crouzon[5] was quick to note that the most deformed craniums are rarely those with the most morbid symptoms.

Craniofacial dysostosis exerts little influence on the duration of life;[5] few ever succumb to intercurrent infections.[1]

Treatment

Early surgical intervention directed toward normalizing the decompensated intracranial hypertension would seem to be logical. As early as 1890, Lannelongue advocated linear craniotomy for craniostenosis.[2] Isolated instances of surgery are reported throughout the literature,[2-4] but it has not been until recent years that surgical intervention has been generally attempted for cases in which the intracranial pressure has become decompensated.

The presence of papilledema is sufficient reason to urge neurologic or neurosurgical help. In the event of blindness and optic atrophy an ophthalmologist bears no burden in advising treatment of the intracranial hypertension. Correction of an associated strabismus offers no unique problem.

Case reports

Case 1

History. The patient, a white boy, aged 5½ years, was first seen on March 22, 1948, with no complaints.

He was born with a peculiarly shaped cranium, deformed face, exophthalmos, and stertorous breathing. There was an unusual increase in the size of the head during the first year of life. There was no history of headaches or convulsions.

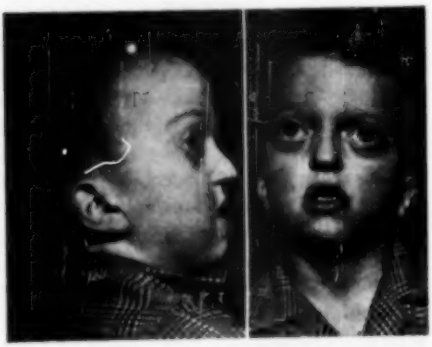

Fig. 1 (Parks and Costenbader). *Case 1.* Preoperative appearance.

A marked bilateral hearing loss resulted from bilateral otitis at the age of seven months. He walked at the age of 17 months and talking has been slow. The parents and two other children are normal.

Examination. The patient was wiry, alert, and normally developed except for his face and cranium. The skull was large in its anteroposterior and vertical measurements, having the shape of a scaphocephalic skull (fig. 1). There was no obvious bossing. A palpable hyperostosed ridge replaced the metopic suture. Digital markings of the skull were seen by X-ray.

The upper face was broad, but depressed, and the nose was prominent and had the contours of a "parrot beak." A high arch to the palate was seen with malocclusion and prognathism. The ears appeared pulled downward and backward. There was equal exophthalmos, hypertelorism, and a divergent tendency.

The refractive error was moderate isohypermetropia and vision was 20/20, O.U. On this first examination there was papilledema of the left disc. The presence of papilledema was questionable on the right disc.

Course. Within six weeks papilledema became more pronounced in the left eye, and a lesser amount of edema made its presence around the right disc.

Operation. On May 10, 1948, a right subtemporal decompression was performed by Dr. J. M. Williams. At the time of the surgery the dura was found to be tense and bulging. Two weeks later the same procedure was repeated on the left. The patient's recovery was rapid and uneventful. Immediately following the surgery there appeared a pulsating mass the size and shape of an egg over the site of each decompression (fig. 2).

Result. To date, eight months after surgery, these masses have remained unchanged, being quite unnoticeable after rest in bed and increasing in size during the day's activities. Papilledema has disappeared, O.U.; however, the left disc margin remains blurred and smudgy. It is felt that this finding represents proliferated glial tissue on the left disc. Vision is 20/20 in the right eye, and 20/40 in the left eye.

Case 2

History. The patient, a three-day-old white girl, was first seen June 25, 1947, upon the request of the pediatrician. The parents and two other children are normal.

Examination. She was a full-term, six-pound infant with bilateral exophthalmos, hypertelorism, divergent squint, high-arched palate, and stertorous breathing (fig. 3).

Course. Her physical development during the first few months was slow and she appeared undernourished. At eight months of age, she was in a state of marasmus at which time she had an associated xerophthalmia and

developed a descemetocele of the right eye. The skull had become deformed but there was no papilledema.

On hospitalization and good general care she improved and the descemetocele retracted, but the temporal half of the right cornea remained opaque and vascularized.

sating, anterior fontanelle which measured two inches in diameter. The ears were pulled downward and tipped posteriorly. The upper face was broad and depressed, the nose was prominent and hooked, and the teeth were maloccluded. A relative prognathism had become apparent.

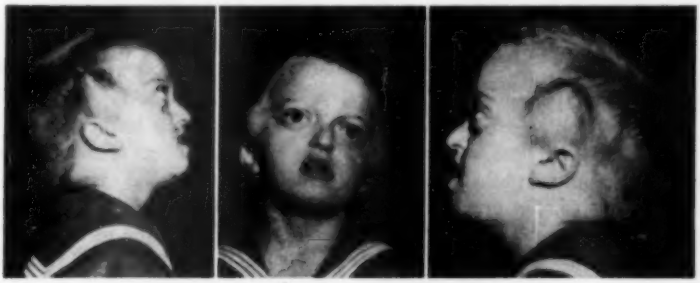

Fig. 2 (Parks and Costenbader). *Case 1.* Postoperative appearance.

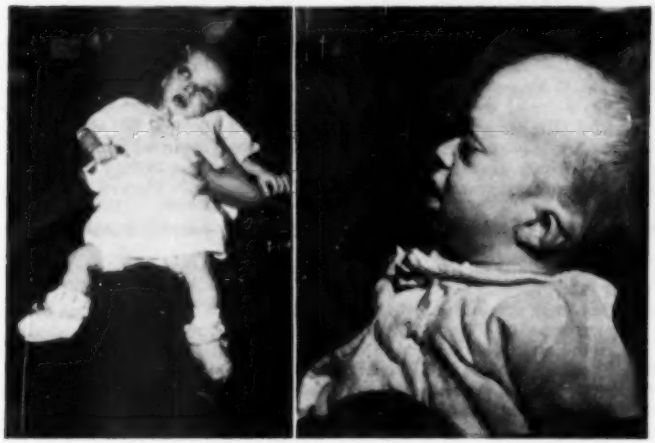

Fig. 3 (Parks and Costenbader). *Case 2.* Appearance of the patient at the age of seven months.

Following this episode the child surprised the parents and physicians by becoming a fat, alert, and happy baby.

At the age of 17 months, the child was husky and walked. The cranium was high in its vertical measurement with frontal and occipital bosses and there was a bulging, pul-

The vision appeared to be normal for each eye, despite the temporal corneal lesion of the right eye. Both discs had sharp borders and were a delicate pink color. The papillary veins were not distended or tortuous.

Comment. The patient is being observed and should the intracranial pressure become

decompensated, neurosurgical intervention will be urged.

CASE 3.

History. The patient, a white boy, aged 4½ years, was seen November 17, 1947, with no complaints.

The child was born with a long head and bilateral proptosed eyes. The history was negative for headaches or convulsions. Both parents were normal.

Examination. The patient was normal mentally and physically except for the craniofacial deformity. There was scaphocephaly, hypertelorism, exophthalmos, and a variable small exotropia. The upper face was broad and depressed, the nose had a "parrot beak" appearance, and there was relative prognathism.

Vision was 20/30, O.U., with an isohypermetropia of small degree. There was bilateral blurring of the disc margins which remained unchanged over a six-month period.

Comment. The parents refused permission for a neurologic or neurosurgical consultation and it is unlikely that they will return the boy for further study.

SUMMARY

Three cases of craniofacial dysostosis (Crouzon's disease) are presented. Surgery performed on the first case in the early stages of decompensating intracranial hypertension was successful in eliminating the papilledema. In the second case the large open anterior fontanelle is probably, for the present, compensating for the intracranial hypertension. The decompensated intracranial hypertension of the third case should have been permitted neurosurgical evaluation.

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BILATERAL PARALYSIS OF EXTERNAL RECTUS MUSCLE IN HYPERTELORISM*

Report of a case with convergent strabismus

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Alexander Brown and R. Kemp Harper[1] in their excellent paper on craniofacial dysostosis classified the craniofacial dysostoses under the following headings: (1) Oxycephaly—high and pointed skull; (2) scaphocephaly—boat-shaped head, keel along sagittal suture; (3) plagiocephaly—skull developed more anteriorly than posteriorly; (4) trigonocephaly—skull developed like a triangle; (5) platycephaly—wide skull with vertical index less than 70; (6) craniolacunia—apparent exaggeration of convolutional markings; (7) hypertelorism—abnormal width between two paired organs.

Of the above groups, the one we are interested in in this report is hypertelorism. This term was first used by Greig, in 1924, to describe an undue separation of the orbits which he believed due to abnormal development of the lesser wings of the sphenoid bones. However, subsequent reports of cases with undue separation of the orbits do not necessarily show changes similar to those reported by Greig in the sphenoid bone. This case report is one in point.

Hypertelorism is usually bilateral, but asymmetry may occur. The deformity is often accompanied by great breadth of the nasal bridge, the bones of which may be massive.

Poor ocular movements, impaired binocular vision, even in the absence of strabismus, abnormalities of the mouth, palate, and hypertrophic gums may occur. Those patients who are mentally retarded usually have an even tempered and gentle disposition.

The authors[1] reported two families comprising five cases, each family affected in at least three generations.

Grant Balding[2] reported six cases with somewhat variable results. Among the undesirable complications he lists are enophthalmos and marked astigmatism at the oblique axes. He concludes, along with Scobee,[3] that: (1) Recession of the internal rectus should be used when a tendon transplant is contemplated; (2) the tendons of the lateral halves of the superior and inferior recti should be sewed into the stump of the external rectus tendon.

J. P. Spencer Walker[4] and Payne[5] both reported cases, and the former author emphasized the almost daily improvement obtained with orthoptic training after surgery.

It is interesting to note the wide variety of surgical procedures advocated for correction of paralysis of the lateral rectus muscle—combined recession and resection, recession of the internus with transplants of the lateral or medial halves of the superior and inferior recti muscles, simple resection and advancement of the externus, transplanting split halves of the lateral rectus, and so forth. All the operations for correcting this defect stem from the original presentation of Hümmelsheim,[6] in 1908, in which he was the first to use the outer halves of the superior and inferior recti in order to gain some lateral movement.

Case report

The following case is reported because of its unusual features and because it shows how surgical procedures decided upon in advance may have to be modified at the time of operation due to abnormal anatomic findings.

History. K. C., a five-year-old white boy, was first seen January 15, 1947, with a history by the mother of a convergent strabismus since birth. There was no family history of strabismus, nor any history of birth trau-

* Presented before Dallas Academy of Ophthalmology and Otolaryngology, December 7, 1948.

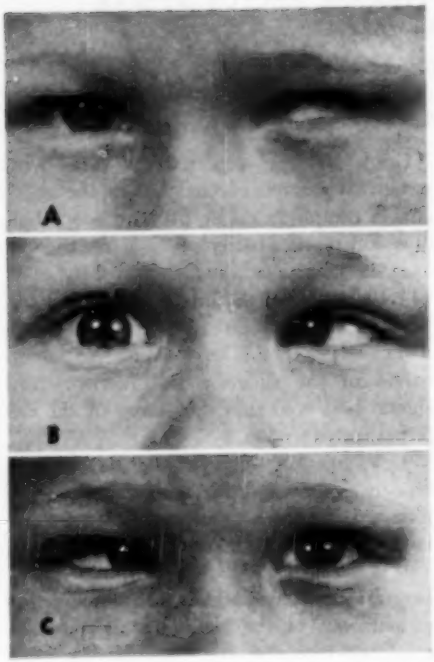

Fig. 1 (Meisenbach). Preoperative views taken on March 5, 1947. (A) Looking straight ahead. (B) Looking to the right. (C) Looking to the left.

ma due to the use of forceps. Besides the convergent squint he presented a paralysis of both external rectus muscles, as well as an overaction of the left inferior oblique. He could alternately fixate with either eye.

The ocular examination was essentially normal except for the muscle anomaly, and it was impossible to obtain any accurate visual acuity on the first visit. Under atropine cycloplegia he scoped a +1.00D. sph. O.U. In the primary position he had an esotropia of about 10 degrees on the perimeter, increasing to 15 to 20 degrees on attempting to abduct either eye. This finding was present both with and without a cycloplegic (fig. 1-A, B, and C).

The tentative operative procedure considered was a 5-mm. recession of the internus of the right eye, with transplantation of the lateral halves of the superior and inferior recti to the stump of the lateral rectus. The actual operative procedure followed on April 14, 1947, was determined by the anatomic conditions found at the time of exposure.

The right internal rectus had an abnormal insertion about 3 mm. from the limbus and was recessed 6 to 7 mm. instead of the usual 5 mm. The Hümmelsheim technique was used on the lateral rectus, with transplantation of the lateral halves of the superior and inferior recti to the stump of the lateral rectus insertion. The lateral rectus was resected 12 mm. and advanced 2 mm. The postoperative course was uneventful, except for a marked chemosis of the conjunctiva which covered the cornea.

On June 16, 1947, the patient showed a good lateral movement of the right eye, al-

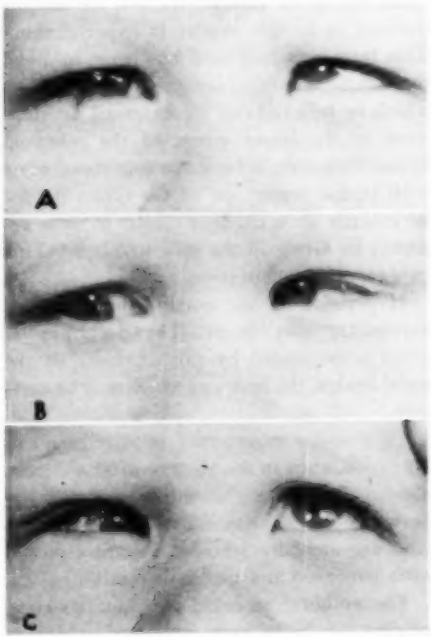

Fig. 2 (Meisenbach). Photographs taken following operation on the right eye, June 16, 1947. (A) Looking straight ahead. (B) Looking to the right. Note moderate abduction. (C) Looking to the left.

though the vertical deviation of the left eye was now more marked than before surgery (fig. 2A). His visual acuity now was: O.D., 20/20; O.S., 20/25. On November 4, 1947, he measured 40 prism diopters of esotropia and 30 prism diopters of left hypertropia.

At this time the tentative operative procedure considered was a 5-mm. recession of the left internus, transplantation of the superior and inferior recti, and a 5-mm. resection and 2-mm. advancement of the externus.

Accordingly on January 15, 1948, the left medial rectus, which was extremely tense and hypertrophied in contrast to the right internal rectus, was recessed 5 mm. The lateral halves of the superior and inferior recti muscles were transplanted below the insertion of the lateral rectus. The latter muscle, which was extremely small and flabby, was resected 5 mm. and advanced 3 mm. The postoperative course was uneventful.

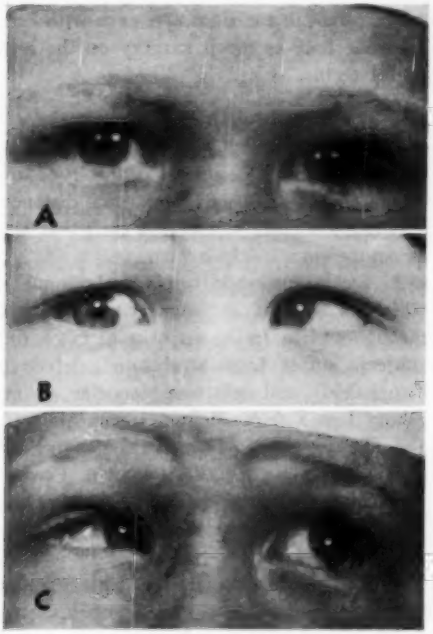

Fig. 3 (Meisenbach). Photographs taken following operation on the left eye, May 8, 1948. (A) Eyes orthophoric in the primary position. (B) Looking to the right. Moderate abducting power of the right eye. (C) Looking to the left. Good abducting power of the left eye. Note marked decrease in overaction of left inferior oblique.

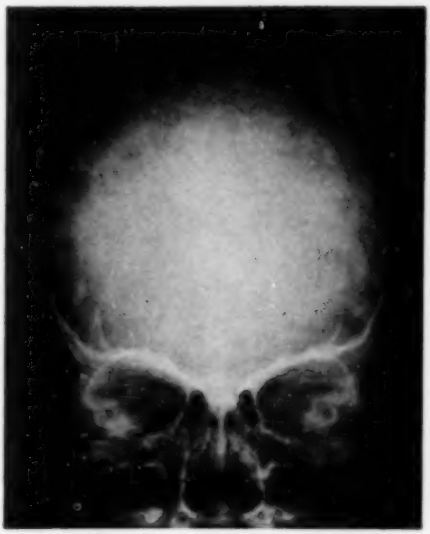

Fig. 4 (Meisenbach). Anteroposterior view of the skull, showing normal cranial vault (R. H. Millwee, M.D.).

On the last visit April 8, 1948, the eyes were orthophoric for distance and near, with and without a correction of a +1.0D. sph. O.U. (fig. 3-A). Vision was 20/20 bilateral with correction.

There was a residual hypetropia on oblique gaze in the left eye, but, in view of such an excellent cosmetic result in a true alternator for the primary position and in view of the high degree of lateral rotation (R.E., 10 to 15 degrees; L.E., 20 to 25 degrees), no surgery on the left inferior oblique is contemplated (fig. 3-B and C).

The X-ray films taken on this last visit were reported by Dr. Robert Millwee as essentially normal, there being no demonstrable abnormal development of the lesser wings of the sphenoid bones (figs. 4 and 5).

Fig. 5 (Meisenbach). Oblique view of the skull, showing normal lesser wings of the sphenoid (R. H. Millwee, M.D.).

Discussion

In Greig's original paper, his case showed overgrowth of the lesser wings of the sphenoid bone. Similar changes were noted by Kersby (1935), Posner and Piatt (1940), and Vorisek (1941). Great variations in the radiologic appearance of the skull have been noted by these and other investigators. The case reported here showed no demonstrable radiologic changes.

This case is particularly interesting because the condition was bilateral, with a high internal squint and an overaction of the left inferior oblique. In addition, the absence of any history of squint in the family, the absence of any possible birth trauma through the use of forceps in delivery, and the negative radiologic findings made the etiology difficult to explain. Certainly, to conjecture the possibility of fetal rickets or of an abiotrophy of the nuclei for the lateral recti makes an interesting speculation. An aplasia or fibroplasia of the muscles themselves must also be considered. It must be remembered that cases of hypertelorism with undue separation of the orbits have been reported, in which no similar changes in the sphenoid bones were demonstrable by X ray.

The abnormal insertion of the internal rectus of the right eye in this patient is the first to be observed by us. There was no hesitancy to operate on all four muscles at one sitting, rather than first doing a recession and resection, and later a transplant of the superior and inferior recti muscles.

The only complication was a slight enophthalmos of the right eye following the first operation, and it was feared that possibly too much resecting of the lateral rectus had been performed. However, this disappeared after a period of 2 to 3 months. The postoperative chemosis of the second operation was much less than that of the first, and the degree of lateral rotation was about 10 degrees more in the left than in the right eye, even with less than one half as much surgery on the left lateral rectus.

Summary

1. Ocular hypertelorism describes a condition which may occur with any type of craniofacial dysostosis. The normal distance between the inner canthi is 3 cm.; that between the outer canthi is 9 cm.

2. Ocular hypertelorism is an abnormality which is evident in infancy and persists throughout life. In the majority of cases, the subjects suffer from strabismus, defective visual fields, and defective binocular vision. About 1 in 5 shows definite mental defects.

3. The etiology of the various types of craniofacial dysostosis is unknown. Premature closure of sutures may be responsible, but this is not always demonstrable by radiology.

4. A case of hypertelorism with bilateral paralysis of the lateral rectus muscles, convergent squint of the alternating type, and overaction of the left inferior oblique is presented.

5. Surgical correction may have to be revised at time of exposure due to abnormal insertions, hypertrophy, or atrophy of the various muscles involved.

6. Orthoptic training may be beneficial following surgery in cases of this type.

Medical Arts Building (1).

I wish to thank Dr. R. H. Millwee for his kindness in supplying the X-ray films reproduced in Figures 4 and 5.

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DIPLOPIA OF PROVOCATION*

Its neurologic significance

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Translator: F. Herbert Haessler, M.D., *Milwaukee, Wisconsin*

We present a description of a new neurologic test, which we have termed "diplopia of provocation," and some brief comments on its mechanism, its varieties, its clinical use, and its future possibilities. It was originally conceived in order to study the latent motor deficiencies which remain after the total clinical disappearance of ocular paralyses. Soon, however, we discovered that its possibilities were more extensive. Thus, it is now possible for us to suggest that diplopia of provocation has a definite place in the clinical neuro-ophthalmic tests.

I. Underlying principles

In a patient in whom an ocular muscle appears to be normal after a more or less prolonged paralysis, a prism of 20 to 45 degrees is placed in front of the eye that was paralyzed (both eyes being open) in such a position as again to produce, as exactly as possible, the initial spontaneous pathologic paralysis. Conditions must be such that the formerly paralyzed muscle is not stimulated to contract. To select the degree of prism we use the lucite prism bar of Dr. Conrad Berens.

The patient must, and this is extremely unpleasant, endure, with both eyes open, the diplopia brought on by the prism for at least 15 to 30 minutes and sometimes even up to 120 minutes. The test is without value unless there is no neutralization of the prism and unless the diplopia exists without intermission during its entire course.

It is at the end of the test, which we call "prismatization," when the prism is taken away, that the diplopia of provocation is produced. Fusion is restored immediately in normal subjects, but a residual diplopia persists in certain old ophthalmoplegias. We are dealing here with a true "diplopia of reappearance" which follows the application of the test prism and survives its removal.

With our colleague, Claude Boudon of Vichy, we made our first observations on a patient who still had convergence asthenopia after temporary ophthalmoplegia of the

* First presented before the Société d'Ophthalmologie de Paris, June 21, 1947.

fourth cranial nerve. As this patient progressed toward complete cure, the duration of the periods of diplopia of provocation lessened and it was possible to follow the gradual straightening-out process.

In so far as we have been able to discover, there is not a single reference to this subject in the literature. Only Comberg (Klin. Monatsbl. f. Augenh., 3:120, 1945) seems to have approached the phenomenon which we have described. His work, however, does not deal with reinvoking a diplopia that has disappeared clinically. On the contrary, through the use of prisms, he reveals the presence of a pathologic condition progressing toward diplopia.

II. Aims

Our test belongs essentially in the general class of tests of provocation and has as its purpose: (1) The study of latent motor deficiences following ophthalmoplegias; (2) a more minute study than is at present possible of the exophorias and convergence insufficiencies; (3) the definition, by the crossing and uncrossing of the diplopia of provocation, of the trend toward aggravation or improvement of latent ophthalmoplegias; (4) the exploration of various important neurologic syndromes of ocular symptomatology which have not been manifest but in which our test of provocation will be able to show heretofore unsuspected oculomotor damage.

In fact, by means of the diplopia of provocation, it should be possible to measure not only the state of the muscle studied, but also the general cause of its injury, whether it was due to syphilis, diabetes, or even to cerebral tumor. Serial examinations indeed permit a true "measured" tabulation of the cause of the paralysis and its degree.

We have been able to establish by clinical observation, that, in the phenomenon we are describing, a true muscular deficiency has reappeared and that it is not a compensatory hypercontraction of the antagonist. Experimentally, by atropinization for example, it is possible to show that accommodation maintains convergence and has absolutely no effect on provoked diplopia.

III. Method

Diplopia of provocation manifests itself only when it has been able to reproduce the initial paralysis exactly and for a fairly long period. Nor does it occur under conditions in which the formerly paralyzed muscle has been put into play.

The choice of the best position to give to the prism to elicit most easily the diplopia of provocation is a point of exceptional interest. The first thought is to place the prism in such a way that the formerly paralyzed muscle must contract to avoid the diplopia created by the provoking prism. If the muscle does not succeed in this, there remains, after this useless and powerful effort, a deficiency which is also exploited by the antagonist and whose expression is itself the diplopia of provocation. This is what some have called the "logical position" of the prism of provocation.

It is by placing the prism in the "illogical" position, that is, in the opposite direction, that we observe the clearest and most lasting diplopias of provocation. Everything occurs, then, as if the recently paralyzed muscle, placed in absolute inaction by the prism during the provocation, regains its contractility only slowly and with difficulty, when the removal of the prism again gives full and complete freedom to the oculomotor antagonists which then carry on without difficulty. Unfortunately, we are not yet sufficiently rich in experiments to draw formal conclusions on this subject.

IV. Duration

The duration of the diplopia of provocation depends on the duration of the application of the test prism, the degree of original paralysis, the time of its clinical disappearance, the degree of progress toward a cure of

its cause, the exact type of the paralysis (homonymous diplopias reappear more easily by provocation than those connected with injury of the adductors), and on the general condition of the subject (for example, mere fatigue or actual illness).

The usual duration of secondary diplopias is about 30 minutes, but we have noted durations of 2, 6, 48, and, once, even of 90 hours. No rule governing the respective durations of prism-induced diplopia and secondary prism-free diplopia can be formulated, but we can affirm that in no case have any unpleasant after-effects been observed. Nevertheless, it takes much persuasion to induce the patient, who is naturally disturbed by the reappearance of his trouble, to submit to the test.

V. Measurement and Varieties

We deal generally with a microdiplopia of not more than one degree. The angle of deviation must be measured with the Maddox cross which is more precise than the perimeter. The latter brings on a troublesome discomfort by the proximity of its arc. One can obtain an approximate measurement with the Maddox rod or with colored glasses.

Practice has taught us that certain diplopias of provocation do not occur except after a specific excitation, perhaps as a result of a long duration of prismatization, or because of the extreme power of the prism, or finally because of the necessary repetition of prismatization.

An important complication that often thwarts our efforts and makes the interpretation of our results more difficult is the habituation to the test prism which appears in the course of experiments among the old ophthalmoplegics who are perfectly stabilized.

To conquer this habituation it becomes necessary to increase the strength of the prism, or to lengthen or repeat the sessions of prismatization.

Two varieties of diplopia of provocation would seem to be most worthy of attention at the present time. The first, which may prove to be of considerable importance to neurologists, is the induced diplopia, so named because the prismatization provokes persistence of double vision after removal of the provocative prism in certain subjects who are neurologically deficient but ocularly intact even though these subjects had never before known double images.

The second, which we call diplopia of selection, permits analysis on a physiologic plane of the various elements of a complex ophthalmoplegia. The least-affected pair of cranial nerves ceases, after a time, to provoke diplopia by its disuse and only the diplopia connected with the most-affected oculomotor nerve persists.

For example: A young woman, apparently cured of an ophthalmoplegia specifically involving the sixth nerve and a part of the third (right superior), reacted by a considerable and confused diplopia of provocation to prismatization of 30 minutes. A quarter of an hour after removal of the prism, the horizontal doubling (sixth pair) disappeared and only the vertical (third pair) diplopia remained. We thus learned that the greatest injury was to the third nerve. Although the diplopia of selection is the most recent possibility our test has disclosed, we are certain there are other possibilities not, as yet, detected or identified.

VI. Observations

By means of the provocative prism test, it has been possible to reëvoke the latent sequelae of paralysis in patients who were apparently cured. This has been done in cases of: paralysis of the oblique that resulted from palpebral focal infection; paralysis of the external oculomotor of diabetic origin; common oculomotor paralysis of traumatic origin; injury of the sympathetic, occurring in the course of treating a frontal mucocele; paralysis of the external ocular muscle after freezing; involvement of the external

oculomotor in facial paralysis following grippe; paralysis of the common oculomotor in three tertiary syphilitics; paralysis of the external oculomotor of glaucomatous origin; paralysis of the common oculomotor after cerebral hemorrhage and after relapse of cerebral tumors.

Nothing is more impressive in an old patient operated for cerebral tumor, with an ophthalmoplegic episode recorded previous to intervention and cured by it, than to see the duration of diplopia of provocation gradually diminish for an identical period of prismatiziation. In this way it is possible to obtain a true measure of the extent of the original pathologic process and the degree of progress toward cure.

Conclusions

We would like to acquaint American ophthalmologists and neurologists with the test of diplopia of provocation because we believe that the test is capable of giving a true measure of the lesion and of its cause.

The fact that, with the diplopia of provocation, one can follow an absolutely silent lesion in the course of routine clinical investigation, give a controllable prognosis at any time, watch the success or failure of a therapy, and, finally, can extend the exploration to affections still without evident oculomotor symptoms makes it seem worth while to us to make our work known and to advocate its general use.

We certainly do not belittle the infinite patience that the application of our test takes on the part of the observer, the good will and absolute confidence that it exacts from the subject observed, the infinite disappointments that this research involves, and the fact that the interpretation of its results is not always immediately accessible.

But the fact that the test will confirm or correct a neuro-ophthalmologic diagnosis makes it seem worthy of the attention of clinicians of whom we ask only that they study it with an open mind and, through experimentation much greater than our own, to give it practical and general evaluation.

91 Rue Sylvabelle.

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RESEARCH IN THE USE OF CURARE FOR OCULAR SURGERY*

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A concept of anesthesia for ocular surgery based on an analysis of the patient, an analysis of the effect of each drug used in the preparation of the patient, and a rational use of drugs for their designed purposes has been proposed by Dr. Daniel B. Kirby, director of ophthalmology at Bellevue Hospital. According to Dr. Kirby, the five criteria for proper anesthesia in intraocular surgery are: (1) Sedation, (2) analgesia, (3) anesthesia, (4) palpebral and global akinesia, and (5) basal or general akinesia. It is the purpose of this paper to discuss the fourth and fifth criteria.

Palpebral akinesia is obtained with some facility by the O'Brien or Van Lint injection of novocain. Although the procedure is not always satisfactory, akinesia of the globe may be obtained with a retrobulbar injection of 2- to 4-percent novocain with or without adrenalin. However, the hazard of hemorrhage may be encountered during this procedure and, once it is, the surgeon hesitates to use this method of obtaining akinesia ever again. In addition, a retrobulbar injection does not always give complete global akinesia.

For these and other reasons, a drug that would promote complete quiet of the globe was sought and, since curare had been used for eight years in anesthesia and for four years in general anesthesia to obtain relaxation of muscular structure for the general surgeon, it was decided to investigate its use in ocular surgery.

CURARE

Curare, a drug having a paralyzing effect at the myoneural junction of skeletal muscle (and of some historic interest), does not uniformly affect all muscles of the body simultaneously. Characteristically it manifests its effects in a quieting or relaxation of the entire body before the ability of muscle groups to contract is lost. From our observations, we would list the progressive involvement of muscle groups in the following manner: The facial muscles become flaccid, followed by ptosis of the lid and paralysis of the levator palpebrae. Next the elevators and depressors of the globe are affected and then the cervical muscles and the horizontal rotators of the globe. The last groups to be affected are those of the extremities, the accessory muscles of respiration, and the intercostal groups.

These stages are not sharply demarcated or distinct but rather overlap. The important observation is that the extraocular muscles are among the first regional muscles affected.

It has heretofore been held that curare has no central depressant or stimulating or analgesic properties. More recently, however, this concept has been considered erroneous, although just what central effects curare possesses is not yet definite.

Prescott, Frederick, and others[1] report an increase in blood pressure due to curare, but Scott, Smith, Brown, Toman, and Goodman,[2] and Cullen[3] report that the blood pressure changes are negligible. In our cases, we found no alteration in the blood pressure in some instances and an elevation of 36 mm. Hg (systolic) and 25 mm. Hg (diastolic) in others. We concluded that this was an emotional response due to apprehension, since the blood pressure changes were less in those patients who received a sedative prior to the test dose of curare.

It must be mentioned that the muscles of deglutition and the cough reflex are paralyzed about the same time that the ocular muscles are affected. This tends to make an apprehensive patient more fearful and is the reason why we believe that the presence of

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respiratory secretions are a contraindication to the drug.

With more than moderate amounts of curare, the tidal volume of air is reduced in the pulmonary exchange and the diaphragm takes over as the only active respiratory muscle. Because of this reduction, patients not receiving preliminary sedation feel the need of taking deep inhalations. In our test cases, however, no clinical observation of anoxemia to the point of change in the normal color of the patient was made. Emphysema and asthma or a history of asthma were also considered contraindications to curare. Myasthenia gravis is also a contraindication to curare for the effect of the drug is greatly multiplied, and the recovery prolonged.

The hazards of curare are in overdosage and in failure to observe the progress of its action as it involves succeeding muscle groups.

Method of administration

Curare when injected intravenously acts immediately, 20 units in one minute being sufficient to detect its effect on the facial muscles. On our test cases the drug was administered at the rate of approximately 20 units per minute until our end point was obtained.

If the drug is given slowly, as described, and the patient is observed for its effect, the beginning of ptosis of the lids will serve as an indication that ophthalmic akinesia is being approached. Ten units more of the drug will produce fair global akinesia, and 15 to 20 units of the drug injected from the point of beginning ptosis will produce surgical akinesia of lids and globes. The total average dose for our purpose is 50 units.

Duration of action

The transitory duration of the drug's action is a safety factor except in myasthenia gravis. From complete paralysis of all skeletal muscles except those of the diaphragm, there is considerable recovery to safety in 3 to 5 minutes. Part of the drug is broken down in the liver and part is excreted as such by the kidneys. Nearly all of the drug is disposed of by the body in 25 to 30 minutes. A patient can walk to his bed unassisted 30 minutes after a completely paralyzing dose.

Antidotes

Bernard described the toxic effect of curare as respiratory paralysis. In fact, it is in respiratory paralysis that the danger of overdosage lies. It has been our practice to have a member of the anesthesia staff on hand during administration of the larger doses of curare, so that a laryngeal or tracheal tube could be passed to supply oxygen if indicated. It was necessary to do this only once and then to aspirate blocking secretions from the trachea rather than to supply oxygen.

Prostigmin[4] in the form of prostigmin methylsulfate (1:2,000), in a 1-cc. solution which contains 0.5 mg. of the drug, has been administered as an antidote because its deterring effect on cholinesterase permits a more prolonged action of acetyl choline at the nerve ending. Up to 1.5 mg. of prostigmin has been used intravenously with an apparent hastening of the recovery period. This, of course, does not supplant the administration of oxygen which is best given under pressure.

Observations of curare's effect and administration

When observed for the ocular effect of curare, subjects showed the following manifestations after 20 to 30 units of the drug had been administered. There was first the relaxation of the facial muscles, after which a beginning ptosis of the lids could be seen. This ptosis was barely perceptible at first and became more easily recognized as we became better acquainted with the drug.

At the time when ptosis is easily recognized, the usual blinking reflex, normally about 16 per minute, is reduced to one half or less in frequency. Ten units more of the drug usually caused a quite noticeable ptosis. The lid would lose its normal palpebral fold and the margin would rest about 1 to 2 mm.

lower over the cornea. This we arbitrarily called the first stage.

At this stage, the globes, normally active in roving excursions with momentary fixations, would come to and hold the primary position, occasionally moving, in a limited fashion, to one field or the other before returning to the primary position again.

The second stage, obtained with approximately 10 units more of the drug, usually showed cessation of these momentary excursions and a more complete ptosis. The globes remained fixed in the primary position. There was disinclination to gaze movements although, on command, they could be made.

The third stage, in which the frontalis could not overcome the ptosis or gaze movements could not be accomplished on command, arrived with the injection of 10 more units of curare.

Calculation of dosage

There is no guide to determining the dosage required to produce the desired results. It was first thought that the muscular component of the body was primarily concerned but this did not prove to be the case. Thirty units produced the signs of the first stage only in one woman who weighed 102 pounds. This same amount caused early signs of the third stage in a woman whose weight was 155 pounds. However, the effects observed in the majority of cases appear with the doses mentioned in the description of curare's effects.

The average amount of curare needed to produce onset of ptosis in 50 cases was 38 units, and approximately 10 units more caused a more complete ptosis and reduced the ocular excursions to a minimum. Beyond these averages there was considerable variation in the amount required to halt ocular movements completely. One man, weight 150 pounds, required 140 units of curare over 11 minutes to halt excursions of the globes; another man (175 pounds) required only 60 units in four minutes to produce the same effect.

In our tests, Squibb's d-tubocurarine chloride was used. It is a purified salt of the active curare containing 20 units per cc., each unit equal to 0.15 mg. of the drug as measured by the rabbit head drop method. Preparations of different companies vary as to potency.

Clinical tests with curare

At Bellevue Hospital a number of patients were given test doses of the drug in order to determine the dosage required to obtain akinesia and to become acquainted with its effects.

One group of 15 subjects who had had no prior medication were administered curare to the point of no movement of the globes upon command. The average amount required to reach this end point was 76 units. Duration of inability to move globes on command averaged nine minutes, the longest period being 15 minutes and the shortest five minutes. Follow movements of the eyes were retained in all cases, as is to be expected, since the reflex is phylogenetically older than the command reflex.

Blood pressure changes were negligible in 10 of the patients; in the remaining five, increases attributed to apprehension were recorded. Intraocular pressure recordings on 20 of the 30 eyes in this group showed a decrease of 2 to 4 mm. Hg. The longest period for observed effects of the drug was 23 minutes in one case.

Curare used with barbiturates

A second group of 15 patients, who had received sodium amytal (0.2 gm.) 1½ hours prior to administration of curare, were observed when the drug was given to the point of no movement of the globes on command. The average amount required was 90 units. The largest dose required was 140 units and the least, 50 units. The longest duration of no movements was 14 minutes, the shortest three minutes.

Blood pressure and intraocular changes were not recorded in this group.

The 30 subjects in the first and second groups received what was considered a large dose of the drug, the intercostals were paralyzed in some instances and, although there was but slight increase (up to 28 per minute) of the respiratory rate, the patients were apprehensive at not being able to breathe deeply.

Succeeding groups of patients were then observed to determine the minimum amount of curare required to produce "quiet eyes."

Twenty-five patients were given 0.2 gm. of nembutal 1 to 2 hours prior to the administration of the curare. The following results were recorded: The average dose needed to cause onset of ptosis and hold the eyes in the primary position was 45 units. This was the minimum dose needed to reach the end point of "quiet eyes." Average respirations in 20 cases were increased by four per minute. Intraocular pressure in 30 of these 50 eyes showed no change in 18 cases and a decrease of not more than 4 mm. Hg in 12 cases.

Twenty-five patients premedicated with phenobarbital (0.2 gm.) two hours prior to a test with curare gave similar results. The greatest amount necessary to elicit ptosis was 60 units and the least 25 units, the average for this group of cases being 42 units. Blood-pressure and intraocular-pressure recordings were variable, although a slight increase in blood pressure was shown and a minimal decrease in ocular tension. Respirations were more shallow and slightly more rapid than normal but not significantly so, the average rate being 28 within two minutes after administration of curare had been stopped.

From our observations of the effect of curare on the extraocular muscles, we determined that the dosage required to halt global movements a sufficient period of time for intraocular surgery was within safe limits of administration of the drug.

Summary

1. A good anesthetic in ocular surgery includes satisfactory akinesia of the eye and of the patient. With present methods this is not always obtained.

2. Curare, a paralyzant drug, affects the extraocular muscles among the first group of muscles involved.

3. Thirty cases in which curare was administered to the point of inability to move the eye on command are presented. The average amount required for this was 83 units, or 4.12 cc., of d-tubocurarine.

4. Fifty cases in which tubocurarine was administered as it would be to obtain "quiet eyes" at operation required an average of 45 units of the drug.

Conclusions

1. Curare, a paralyzant, having its effect at the myoneural junction affects the extraocular muscles before the muscles of respiration.

2. Global and basal akinesia may be produced by curare.

3. The safety factor in curare administration rests on close observation of the drug's progressive effects.

4. Curare in doses sufficient for akinesia in ocular surgery may slightly elevate the blood pressure, lower the intraocular pressure, and produce a minimum effect on respirations.

5. Curare in safe dosage may be employed as an akinetic in ocular surgery.

1 Hanson Place (5).

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Discussion

Capt. Richard Stern (Brook General Hospital, San Antonio, Texas): Has this drug been used locally in the orbit combined with the retrobulbar injection?

Dr. Harold Gifford (Omaha, Nebraska): I think this is a very interesting approach to this problem and should be valuable in certain cases. I tried some curare on rabbits several years ago when I started work on a method of retrobulbar akinesia. I obtained some curare from Dr. Ross McIntyre who did the original work on intocostrin.

I used the retraction syndrome as a measure of the reflex activity in the rabbit. I found that the lethal dose was so close to the loss of reflex activity that I felt it was too dangerous to use clinically. I believe Dr. Roche stated that the dose to produce a loss of reflex activity was almost double the dose to produce the loss of voluntary activity. I would like to ask the author how complete the akinesia was with the 45-unit dose?

With the deep retrobulbar injection of novocain, using a 5-cm. needle instead of the usual 3.5-cm. needle, complete akinesis for both voluntary reflex and activity could be obtained in about 75 percent of the injections. With this method there is slightly more danger of intraorbital hemorrhage. I, personally, would rather have the intraorbital hemorrhage than collapse of respiration during a cataract operation.

Dr. David G. Cogan (Boston): Perhaps this is in anticipation of the reply of Dr. Roche.

Dr. Lemoine and I, several years ago, tried retrobulbar injection of curare, feeling, as the essayist did, that it is ideal for the extraocular muscles. We were much disappointed and surprised that the dose we found necessary to produce paralysis in the extraocular muscles from orbital injection on one side had to be great enough to cause a paralysis in the opposite eye about the same time, and this was fairly close to the lethal dose, as Dr. Gifford has suggested. Tentatively we assumed that the absorption from the orbit must be greater than the diffusion within the orbit. In any case, we found that the local muscles were not paralyzed by the injection, as we had anticipated.

Dr. Alson E. Braley (New York): In what progression were the ocular muscles involved—or were they all involved simultaneously?

Dr. Walter B. Lancaster (Boston): I should like to ask about the mental state of the patient, and the apprehension. When the patients feel themselves losing control of their muscles are they apprehensive?

Secondly, have there been any serious threatened lethal effects? What is the margin of safety? How wide a zone is there between the desire effect and the lethal effect?

Dr. William B. Clark (New Orleans): Perhaps we were very fortunate in having for a general anesthetist, a former professor of pharmacology at the University of Wisconsin Medical School, Dr. Thomas C. Sherwood. He worked with us in our preliminary experiments with curare. After being in preclinical medicine for many years, Dr. Sherwood decided he perferred to go into clinical medicine, and is now practicing anesthesia in our city. It was from him that I received my initial encouragement to experiment clinically with curare as an aid to basal and local anesthesia in cataract surgery.

Dr. Sherwood had used the drug experimentally in animals a great deal before it had been purified, and felt it was a very dangerous drug; however, since the purified form has become available he has been using it freely in general anesthesia and feels it is much less dangerous now that it has been more completely purified. In fact, it was he who gave the drug to the patients when we began using it and, after its successful use in a few cases, he convinced me it was not necessary to have a general anesthetist administer the drug along with a local anesthetic during a cataract operation.

Dr. Sherwood's instructions to us were

that he felt the drug was safe as long as it was administered in doses of not over one-half a unit per pound of body weight, provided this dosage was administered at a rate of 10 units per minute in broken doses of 20 units per dose.

We have now been using it for several months and have been using it in the following types of intraocular surgery for more complete immobilization of the globe: Cataract extractions, glaucoma operations, and keratoplasties. We use it in combination with local and basal analgesia; however, we do not use as much local as we previously did, particularly in regard to the retrobulbar injection of 4-percent procaine. We now inject 1 cc. instead of 2 cc. Otherwise, we use about the same amount for our akinesia and lid anesthesia.

We have used it on patients in the age range of 30 to 92 years. We have used it in one asthmatic, knowing at the time it was contraindicated, but this was in the case of an emergency operation for glaucoma. The patient was a very high-strung, emotional individual, and we felt it would be almost impossible to get the cooperation of the patient to do the glaucoma surgery without the use of curare. We obtained the desired results during the surgery without producing an attack of asthma, but as a safety measure, at the conclusion of the surgery, we gave her immediately an injection of prostigmin and we were very gratified to see that all the effects of the curare had disappeared at the end of 10 minutes.

To date we have used curare in 44 cases of major ocular surgery in patients of varying physical and emotional states, and I am glad to report we have had no untoward effects. This, in my opinion, is an excellent paper in clinical research and Dr. Roche is to be congratulated on his presentation.

DR. JOHN R. ROCHE (closing): In answer to Captain Stern's question: No, the drug has not been used locally in the orbit or retrobulbarly. The drug's effect is systemic when injected intramuscularly; it does not affect those muscles or that muscle group locally, but acts systemically. It must be absorbed into the blood stream and thus carried to the orbit. It would be very hard to hit the specific nerve end that you would want to hit with it in order to have it act.

There is much that is not known about its action and about how it blocks the action of choline. It has merely been said that its effect is at the myoneural junction, and that is why, in Dr. Cogan's case, he found that if enough of the drug were injected intraorbitally or retrobulbarly to produce paralysis in one eye, there was a systemic effect to the extent of a paralysis in the other eye.

The effect of curare is on reflex motion first, and voluntary afterward, because it does paralyze the muscle groups. The dose to abolish these reflexes is safe—pardon me; Dr. Gifford said, and I wish he would correct me if I am wrong, that this abolishes voluntary movements first, and reflex movements afterward.

DR. GIFFORD: That is what you said.

DR. ROCHE: You are right, sir. The eyes will come to rest in the primary position before the reflex motions are gone. The follow reflex which comes after the command reflex to move the eyes is not paralyzed until much later, until a large dosage is given; but a patient must have anesthesia and sedation. They will have sedation and will be quiet on the table. They will have anesthesia, and curare is used merely to halt the motions of the globe. It is not recommended in every case.

There are only a relatively few cases in which you find that the patient on the table has not responded to his premedication and is quite restless, tense, with the neck stiff, the chin up, the back arched. The dose necessary to relax all this and to hold the eyes from reflex stimulation in the primary position is about 45 units, or not more than 50 units. We have seen used on the table up to 60 units with no embarrassment of the res-

piration. The respiratory rate is increased, but the patient, being sedated, is not aware of loss of this sense of wanting to take a deep breath. That was in patients whom we tested without sedation.

How complete is the akinesia? It is complete. The eye is operated on without any other akinesia, and the duration has been from 8 to 15 minutes.

Dr. Braley asked in what progression are the extraocular muscles involved. They are not all involved simultaneously. First the levator is involved, then the elevators and depressors, and then the cervical muscles are involved before the horizontal rotators are involved. After that the extremities, then the accessory muscles of respiration, lastly the intercostals are involved.

So, if the progress of the action of the drug is observed, you can prevent going so far as to involve the extremities. You can ask the patient to raise his arm, or you can watch for enforced cessation of movements. When the eye is brought into the primary position, if the injection is stopped there (and that is another reason for giving it intravenously rather than retrobulbarly), you have control over it and you can stop your injection there, because there is no dose to curare. It is given to the point desired, and then administration is stopped. It cannot be a calculated dose.

Dr. Lancaster wanted to know about the apprehension of the patient, which I think I have answered. If the patient is sedated he is not aware of the reduced excursions of the respirations.

There have been no lethal effects, and these can be avoided by watching the progress of the drug. The tip-off on the amount of curare to be given—the dose being approached that you are desirous of giving—is the onset of ptosis of the lid. That is why I stressed that. Ten units more of the drug will halt the eyes in the primary position.

Dr. Clark mentioned earlier that, when Intocostrin was used, there were side effects thought to be due to the vehicle; that is so. The more purified drug has no side effects other than its actual pharmacologic action.

The definition of "unit" is that amount of curare necessary to cause head drop in the majority of a group of test animals when they are rotated, one group today and one group tomorrow, and the first group again on the third day. It is the minimum amount of curare necessary to produce head drop in the majority of those groups. It is called the head drop cross-over method of determining the unit.

Ophthalmic Miniature

When toward night time, the daylight falling subdued through a window, a burning candle is so placed that a ruler or pencil will cast two shadows on a sheet of white paper, one from daylight, the other from the candlelight, each illuminated by light from the other sources, one of the shadows will appear yellow, the other a vivid blue.

Goethe, *On Colored Shadows*, 1792.

THE USE OF INTRAVENOUS MORPHINE IN OCULAR SURGERY

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The proper use of intravenous morphine as a basal anesthetic agent is invaluable in ophthalmic surgery. Although it can be argued successfully that all preoperative narcotics have physiologic drawbacks, to condemn morphine as a chief offender is to ignore the accumulated literature on the intravenous use of this drug in medicine and surgery.

MORPHINE AS A GENERAL ANESTHETIC

Any discussion of the use of intravenous morphine as a basal anesthetic recalls the interesting medical history of this drug in general or surgical anesthesia.

According to Lewis,[1] Schneiderlin, in 1900, first reported the use of a combination of morphine and scopolamine hypodermically for surgical anesthesia. By repeated injections of morphine and scopolamine in the ratio of 1 to 25, he was able, in many cases, to raise the threshold of pain to the point where he could perform major surgery. The frequent occurrence of complete amnesia for the operative procedure appealed to the medical profession.

In 1903, Teinbuchel (Lewis[1]) applied this form of anesthesia to obstetrics, and European clinicians made the method, known to the laity as "twilight sleep," the continental vogue in obstetrics. Early in this period Lewis observed the use of "twilight sleep" in the obstetrical pavilions at the University of Freiburg. He adapted its use to otolaryngology.

In 1923, Lewis reported his individual experience covering more than 15 years of use with the morphine-scopolamine combination as a modification of hypodermic narcosis for basal anesthesia in ear, nose, and throat cases. He gave prior recognition to Dr. Myron Metzenbaum who, in 1900, had begun to use the combination for ear, nose, and throat surgery. Lewis stated that he had used the combination in all types of "bad risk" patients. He had operated many patients under this narcosis whom he would have hesitated to operate under general inhalation anesthesia. In relatively rare instances, Lewis encountered certain disquieting symptoms such as tremor, tachycardia, and palpitation, but never to a degree that interrupted the surgical procedure. He remarked that occasionally excitement and delirium of mild degree had been encountered. Rarely, slight cyanosis was observed. In several cases, late postoperative nausea followed the hypodermic injection of morphine and scopolamine. He felt justified in concluding that in the use of morphine and scopolamine hypodermically he had witnessed no severe side effects.

In 1907, Suker[2] discussed for the first time the use of morphine and scopolamine in ophthalmic surgery. Following the method used more or less extensively by certain general surgeons, he induced general anesthesia by repeated hypodermic injections of a combination of morphine sulfate and scopolamine hydrobromate. Suker applied this method to cases of acute glaucoma, cataract extraction, keratectomy, and enucleation. He noted the absence of excitement either before or after operation, absence of muscular rigidity, and the retention of sufficient consciousness on the part of the patient to obey the orders of the surgeon.

Three injections of morphine sulfate (gr. 1/6) and scopolamine hydrobromate (gr. 1/150) were made, one hour apart, beginning 2¼ hours before the time set for the operation. Suker warned that the method was not entirely free from danger since six deaths in 3,000 anesthesias had been reported in the literature.

Segelken[3] reported no untoward results in

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a series of over 100 ocular surgical cases in which the combination was used.

Stuelp's[4] experience with the method in 100 cases led him to state that, despite occasional failures, the plan had merit. He found that, in glaucoma, complicated cataract, and other difficult operations on the eyeball, the operation was simplified by "quieting the patient," and observed no bad effects on the general condition of the patient even in the presence of systemic diseases.

Stuelp used morphine sulfate (gr. 1/6) and scopolamine hydrobromate (gr. 1/150) three times, one hour apart. In cases in which he considered successful narcosis had been obtained, consciousness was much obscured but not abolished and energetic questioning could elicit correct answers. He found that no expression of pain occurred during corneal incision, iridectomy, cutting the muscles, or the insertion of sutures. He reported that the movements of the eyeball were usually carried out correctly, and in a quiet and certain manner.

In Stuelp's 100 cases, good narcosis was obtained in 45; in 29 it was incomplete but sufficient to carry out the operation; and in 26 it failed. In some cases it produced slight mental excitement and marked increase of sensibility so that chloroform was required to finish the operation.

Hare[5] insisted that this anesthesia was not entirely devoid of danger and that its use alone for surgical narcosis was not justifiable, while H. C. Wood, Jr.,[6] made the extreme statement that "the method is scientifically irrational, and inasmuch as it has shown a mortality of one per 1,000, and in 69 percent of the cases the anesthesia has been unsatisfactory, we think it must either be a very bold or a very ignorant surgeon who will persist in its use." Wood failed to support his statement with convincing case statistics.

Casey Wood[7] reported its use in iridectomy for acute glaucoma, enucleations, lid operations (ptosis, entropion, and so forth), and Elliot trephining operations "with conspicuous success." He remarked that the total lack of apprehension on the part of the patient "compels the attention of all serious-minded surgeons."

The use of repeated hypodermic injections of morphine sulfate and scopolamine hydrobromide for general anesthesia gradually faded into disrepute and finally into disuse.

Survey of use of morphine in preanesthesia

In recent years Vouters[8, 9] has urged a combination of scopolamine, morphine, and ephedrine as a hypodermic injection for "basal anesthesia in ophthalmic surgery." By this means of preanesthesia or prenarcosis he proposes a method of inhibiting or simply slowing down the cerebral functions, leaving to local anesthesia the task of inhibiting the reflex channels. He refers to the combination as S-M-E which he employs in the form of a French proprietary drug called Nargenal. Vouters claims that ephedrine, as an excitant of the central nervous system and the respiratory center, opposes the depressant effects of morphine on the respiratory center without diminishing the narcotic effect of the morphine-scopolamine association. He strongly urges this form of basal anesthesia which he feels is a "supplementary trump-card" in the hand of the ophthalmic surgeon. He uses the method for all types of extraocular and intraocular surgery.

The first reference to the intravenous injection of morphine was recorded by Nussbaum,[10] in 1865. He accidentally injected two grains of morphine acetate intravenously into himself. He immediately experienced an alarming train of symptoms and described in detail the transient sensations of tinnitus, scintillating scotomas, severe pain over the scalp, substernal pressure, and marked tachycardia. Intravenous injections of morphine acetate in three other patients produced the same manifestation. Nussbaum made the same observation about these toxic effects that have been made by subsequent investigators; namely, that if the morphine were in-

jected slowly, these symptoms would occur rarely, if at all. Reports appeared in the literature which seemed to bear out Nussbaum's theory that, in those instances when patients manifested a toxic reaction immediately following hypodermic injection, an accidental intravenous injection had been made.

In analyzing these reports two factors had to be considered. First, as Nussbaum himself observed, if the intravenous injection of morphine were made slowly, side reactions were much less likely to occur. Second, the preparation used at that time was usually the acetate salt of morphine which is unstable and could conceivably cause the reaction because of its change in composition.

These damaging observations on the intravenous use of morphine made the medical profession skeptical. For the next 25 years the use of morphine intravenously was restricted to pharmacologic experimentation on laboratory animals. Its clinical application was scarcely commented on in the literature, although it was undoubtedly being used by some physicians during this period.

Use as a therapeutic agent

The publication of Manhenke's[11] work in 1925 stimulated renewed interest in the study of intravenous morphine. He reported his experiences with intravenous morphine sulfate in a wide variety of medical and surgical conditions. He was the first clinician to realize its full potentialties as a therapeutic agent. He described excellent results obtained in cases of biliary colic, painful joints, reduction of fractures and dislocations, tabetic crises, change of dressings, and as a basal anesthetic agent.

Manhenke claimed that the duration and intensity of effect is longer and greater in intravenous injection than when the drug is administered subcutaneously. This claim was denied by Seevers and Pfeiffer[12] who found that, after subcutaneous injection of 10 mg. of morphine sulfate, the maximum analgesic effect appeared in 60 to 90 minutes; after intravenous injection it developed in 20 minutes, but that both the degree and the duration of the effect were less than with subcutaneous administration.

Wolff[13] and others confirmed these observations and further found that, with subcutaneous doses of 0.5 mg. to 15 mg., the elevation in the pain threshold was proportional to the dose—that is, the threshold was increased 10 percent by 0.5 mg., 32 percent by 5 mg., 47 percent by 8 mg., 71 percent by 15 mg., but only 93 percent by 30 mg. This increase in pain threshold was continued over six hours for 8 mg. and not quite seven hours for 15 mg.

In 1938, Salzer[14] published his experience of 20 years in the use of intravenous morphine for therapeutic purposes "without a single regrettable incident." He found the procedure a life-saving measure in certain cases of coronary occlusion and acute edema of the lungs. In 1930, Salzer[15] had previously cited the advantages of administering morphine sulfate intravenously for therapeutic purposes. He remained under the mistaken impression that his paper was the first reference in the literature to the use of this procedure therapeutically. Manhenke's work, published in 1925, antedated Salzer's publication by five years.

Survey of literature

In 1943, Presman and Schotz[16] presented a critical analysis on the use of intravenous morphine. All available references were included in an exhaustive bibliography. They kept careful records in 100 unselected cases in which intravenous morphine sulfate was administered for both diagnostic and therapeutic purposes. Each patient was questioned concerning the presence of any side effects such as dizziness, nausea, weakness, substernal pressure, tinnitus, and so forth. In certain instances the injection was stopped momentarily and then continued at a slower rate. They agreed with the work of earlier investigators who were practically unanimous in their conviction that, if the intra-

venous injection of morphine sulfate were given slowly, the side effects are usually mild and transient. The chief symptoms were found to be dizziness, tinnitus, and a flushing of the skin.

Use as an analgesic agent

Presman and Schotz singled out the impressive work of Betlach[17] who demonstrated the value of intravenous morphine for analgesia in 100 selected cases at the Mayo Clinic. No severe side reactions were encountered in this series. Betlach[18] states that he has continued to use morphine intravenously without untoward effects since his paper was written. He has subjected himself to the procedure and he warns that the feeling of numbness, tingling, and constriction in the chest may be alarming to some patients. He suggests that it is wise to warn them of the possibility of such sensations.

Presman and Schotz[16] drew attention to the fact that by far the most striking demonstration of the value of intravenous morphine in anesthesia has been as an adjuvant to local infiltration and nerve blocks. Physiologically morphine acts as a powerful cortical sedative.

Lundy,[19] Brace,[20] Betlach,[17] and others have favorably commented on the psychic sedation gained in preparation for the dreaded local infiltration.

Presman and Schotz[16] noted that any tension, either physical or mental, disappeared almost immediately on intravenous injection of morphine sulfate. They commented on a generalized relaxation of the entire musculature. Tense, apprehensive, and restless patients became very quiet and frequently euphoric.

The calm and euphoric condition of the patient when intravenous morphine is given 20 minutes prior to the injection of the local anesthetic is of inestimable aid to the surgeon. It is recognized that one of the principal causes of so-called failures in regional anesthesia is the patient's unnerving expectancy of being hurt, rather than the experiencing of any actual pain. Not infrequently this factor fails to be compensated for by the customary hypodermic, especially in the case of the highly nervous and neurotic patient. The calming influence on the patient extends itself to the surgeon.

Batterman[21] reminds us that the majority of analgesic agents exert their main action within the central nervous system. Hypothetically the analgesic may alter the transmission of the pain impulse from the periphery to the cerebral cortex where the consciousness or awareness of the pain is manifest. The cerebral cortex is the most important. Not only is this the highest level for normal appreciation of pain, but this perception may be altered by other cortical centers. Thus, an individual under excitement or emotional stress may not be aware of a painful wound. Those drugs which possess a marked psychic effect on the individual are the most effective analgesics. Thus, it is commonly accepted that the patient is still aware of pain, but he is no longer perturbed by its presence. It implies that fear and its associated implications are decreased or abolished. This may explain why morphine continues to exert an analgesic effect long after tolerance to the peripheral pain threshold has fallen.

Necessity of slow injection

Presman and Schotz[16] repeatedly emphasized the necessity of injecting morphine slowly when the intravenous route is used in order to minimize side reactions. In their study of 100 cases the undesirable side effects, listed in an accompanying table, were few and transient. At no time was it necessary completely to interrupt the injection.

The one reaction that might be considered severe occurred in a 62-year-old woman, weighing 65 pounds, markedly cachectic, and suffering from masked hyperthyroidism. The patient was given morphine sulfate (gr. 1/6) intravenously. Respiratory depression accompanied by cyanosis and finally cessation of respiration ensued. The condition responded

promptly to the administration of 10 mg. of ephedrine sulfate intravenously.

Baird[22] and Dillon[23] have both warned that morphine has a tendency to produce more marked respiratory depression in the aged than in the younger patient, particularly if debilitating illness is present.

Respiratory embarrassment

Smith and Schotz[24] state that it is almost instinctive to think of morphine as an agent capable of dangerous depression of the respiratory center and that the use of the intravenous route would possibly enhance this action. They argue that this is not the case; that in proper dosage no untoward results will occur. They observe that, if the intravenous injection of morphine sulfate and sodium pentothal, both depressants of the central nervous system, does not produce respiratory embarrassment, one need not be concerned over the so-called hazards of morphine given intravenously.

Leigh[25] believes that there is evidence to show that scopolamine and atropine decrease some of the untoward effects of the opiates, particularly nausea and respiratory depression. Like morphine, scopolamine depresses the cerebral cortex and produces amnesia.

Adriani[26] states that scopolamine enhances the cortical depression of morphine, when used with morphine, without depressing respiration. It should be remembered, however, that scopolamine is not an analgesic. Baird[22] feels that scopolamine is a drug which must be used with caution in the aged since it may produce euphoria to a degree that makes coöperation on the part of the patient difficult.

Nausea and vomiting

If the precaution of slow intravenous administration is taken, nausea and vomiting are almost consistently absent according to the observations of Betlach,[17] Presman and Schotz,[16] Smith and Schotz,[24] and other investigators. Betlach[17] believes that vomiting follows intravenous injection less frequently than subcutaneous administration because the vomiting center is depressed more rapidly by the former method.

Minimal movement of the patient after he has received morphine has been emphasized by various investigators. Jones and Chapman,[27] working on the problem of analgesia when pain was artificially produced, found that nausea and vomiting were precipitated in practically every instance by the subject's attempt to walk after morphine had been administered hypodermically. The work of Drew[28] and others indicated that the movement of a "morphinized" patient from the supine to the sitting or semi-erect position may be followed by vascular collapse, particularly in elderly patients.

Advantages of intravenous administration

Betlach[17] lists several advantages of the intravenous method of administration over the subcutaneous method: (1) The full analgesic effects are obtained quickly; (2) the drug can be given at the moment it is needed; (3) the dose may be regulated accurately. Betlach describes in detail his technique of preparation and administration of intravenous morphine. He injects a small amount of the solution very slowly, permitting any idiosyncrasy to manifest itself by the time it reaches the vomiting center. He then injects the remainder of the drug slowly until the desired effect is obtained.

All investigators except Jacobj[29] are in agreement that there is no greater danger from administering morphine sulfate by the intravenous route than by the subcutaneous route.

It is interesting to note that Light and Torrance,[30] working with addicts, injected huge amounts of morphine sulfate intravenously with the appearance of only mild symptoms. One patient received 30 gr. intravenously in 2½ hours, the previous normal dosage being 17 gr. in 24 hours. Chemical studies of the blood, electrocardiographic tracings, pulse, and respiratory rates were recorded. There were no significant changes.

Side reactions

Smith and Schotz[24] consider the intravenous method of giving morphine sulfate as both safe and efficacious even in the rare instances where hypersensitivity to the drug exists. They state that, after a few minims of the solution have been given intravenously, the operator should question the patient as to the presence of any side effects, such as dizziness, tinnitus, nausea, or a sense of substernal pressure. Should any of these symptoms arise, the injection should be momentarily stopped, and then resumed after the symptoms have disappeared. In several hundred administrations they had never found it necessary to discontinue completely the administration of the drug because of the severity of side effects.

These investigators contend that the factor of sensitivity or allergic response to the drug has been greatly exaggerated. They state that, even if an individual is sensitive to morphine, it will be discovered after the administration of the first few drops and that a reaction of severe proportions is less likely to occur under these circumstances than when a large dose is injected indiscriminately into the subcutaneous or intramuscular tissues.

Warnings may be found in the literature on the adverse effects of morphine sulfate. Batterman[21] reminds us that spasm of the trigone muscle of the urinary bladder with urinary retention is not uncommon. Elderly man with hypertrophied prostates, in particular must be observed carefully for symptoms of uremia. Spasm of the bronchial musculature in the majority of patients is of no consequence, but may be dangerous if the patient has bronchial asthma. Examples of the seriousness of this action and the possibility of sudden death of the patient have been cited by Baughan and Graham.[31]

Batterman emphasizes his warning that morphine cannot be administered to all patients with equal safety. In addition to those conditions already mentioned, there is the marked sensitivity of infants and the increased reactivity of the aged. Morphine must be used with caution in patients with liver disease or hypothyroidism. The occurrence of intense pruritus and urticaria may be very disturbing. He concludes his clinical evaluation by agreeing that, although morphine is a potent, efficacious analgesic, it possesses many adverse pharmacologic actions.

Weatherly[32] reminds us that "it is still generally accepted as an empirical fact that the alcoholic patient tolerates morphine poorly." Ausherman[23] shares this opinion.

Comparison with barbiturates

The use of the derivatives of barbituric acid to obtain adequate preoperative medication in intraocular surgery under local anesthesia has proved unsatisfactory. The barbiturates are notoriously unreliable. Baird[22] has pointed out that derivatives of barbituric acid are, as a rule, tolerated very poorly by the aged. He feels that their administration should be omitted in elderly patients because of their depressant effects.

Leigh[25] has emphasized the fact that the barbiturates are hypnotics. They do not possess analgesic properties, nor do they produce psychic sedation. Undesirable side effects include apprehension, agitation, delirium, vasomotor collapse, and respiratory failure. Nausea and vomiting not infrequently accompany gastro-intestinal intolerance to the drugs.

Smith and Schotz[24] state that patients under the influence of morphine sulfate are considerably more coöperative than those under barbiturates, and are less inclined to be excitable or uncontrollable.

Analysis of cases

We have made a careful analysis of 163 consecutive ocular cases, operated under local anesthesia, in which intravenous morphine sulfate in combination with scopolamine hydrobromide was used as the basal anesthetic agent. This was supplemented by the usual topical and infiltration anesthesia

of pontocaine and novocaine. In all but three of these cases intraocular surgery was performed.

The intraocular cases included: 120 intracapsular cataract extractions, 15 extracapsular cataract extractions, 12 Elliot trephining operations, 4 iridectomies, 2 cyclodialyses, 4 retinal detachments, and 3 intraocular foreign bodies.

The three extraocular operations included two dacryocystectomies and one squint. The age groups of these patients were:

Age Groups	Number
20-30	3
30-40	5
40-50	9
50-60	52
60-70	68
70-80	20
Over 80	6

The striking absence of severe side effects is shown in Table 1.

TABLE 1

Occurrence of side reactions following the injection of intravenous morphine in 163 ocular surgical cases

Side Reactions	Number of Cases
Dizziness	
a. Mild	7
Precordial pressure	
a. Mild	9
Tachycardia	
a. Mild	8
Headache	
a. Mild	5
Respiratory depression	
a. Mild	6
Nausea	
a. Mild	4
Vomiting	0

Dosage and procedure

The first 100 cases received a test dose or "pilot dose" the evening before surgery to rule out morphine sensitivity or idiosyncrasy. This intravenous medication consisted of morphine sulfate (gr. 1/6) and scopolamine (gr. 1/150). No case of morphine sensitivity was encountered. This safety precaution was finally abandoned as an unnecessary measure. Instead, the patient was simply given nembutal (gr. 1½ to 2¼) on retiring the night before surgery. On the morning of surgery it has become our established practice to give the preoperative medication 20 minutes before beginning local infiltration. Psychic sedation is obtained in 10 minutes by the intravenous route while full analgesic action takes place in 20 minutes.

Reactions encountered

In the first 88 cases no ephedrine sulfate was employed in the intravenous combination. In this group, six cases of mild respiratory depression were noted. In each case morphine sulfate (gr. 1/4) and scopolamine hydrobromide (gr. 1/100) had been administered. In each case respirations dropped to 6 to 12 per minute and moderate cyanosis was evident. After ephedrine sulfate had been added to the combination of morphine and scopolamine for the last 75 cases, only minimal signs of respiratory depression manifested themselves.

One of our patients, a 64-year-old woman, was a confirmed drug addict, using dilaudid in large quantities hypodermically. She proved to be no problem from an operative standpoint.

Another patient, a 64-year-old physician, was certain that he was sensitive to morphine. He claimed that the smallest dose of morphine administered hypodermically would cause him severe nausea and persistent vomiting. He showed no evidence of morphine idiosyncrasy on intravenous injection of morphine.

One chronic alcoholic, a 68-year-old seaman, reacted entirely satisfactorily to intravenous medication on two occasions.

Three elderly cataract patients, a man, aged 76 years, and two women, aged 67 and 83 years, apparently had delayed scopolamine reactions 12 to 16 hours following surgery. These reactions were characterized by confusion, disorientation, and attempts to get out of bed. These adverse reactions were

transient, but alarming enough to keep the nursing staff alert to such a possibility.

Like all other ophthalmic surgeons we dread having to cope with a "restless eye." This type of aimless, intermittent nystagmoid movement is found more frequently in the apprehensive, obese, plethoric type of individual, especially in the middle aged group (40 to 50 years). Our experience with the use of this preoperative medication in this annoying and trying type of case has been particularly gratifying.

Preparation of solution

For our purpose, the ideal intravenous combination seems to have been reached by making a sterile solution that contains morphine sulfate (gr. 1/4), ephedrine sulfate (gr. 1/6), and scopolamine hydrobromide (gr. 1/200) to each 4 cc. This solution is prepared under sterile conditions and placed in 20-cc. vials in the manner described in our previous article.[34] It is injected at the rate of 1 cc. per two minutes, using a hypodermic needle. Patients above 70 years of age are given 2 cc. of the solution intravenously (morphine sulfate, gr. 1/8, ephedrine sulfate, gr. 1/16, and scopolamine hydrobromide, gr. 1/400). To patients under 70 years of age, 3 cc. of the solution (morphine sulfate, gr. 3/16, ephedrine sulfate, gr. 3/24, and scopolamine hydrobromide, gr. 3/400) are given. In patients under 55 years of age this preoperative medication is frequently supplemented by 2 cc. given at the actual time of surgery if any signs of restlessness or apprehension remain. By waiting 5 to 7 minutes, the desired effect has been obtained. In only one case did this measure fail. In this case it was necessary for the anesthetist to administer a small amount of sodium pentothal intravenously before we felt it was safe to continue with the operation.

Occasionally, minor discomfort is experienced on insertion of the superior rectus or "bridal" suture despite the use of this type of basal anesthesia. However, in our series of cases, pain on iridotomy, iridectomy, and extraction of the lens has been completely eliminated. Amnesia is almost complete because many patients undergoing surgery for cataract on the second eye, remembered little or nothing of the first operation.

Conclusion

1. A series of 163 consecutive ocular surgical cases, operated under local anesthesia, in which a morphine and scopolamine solution was administered intravenously as the basal anesthetic agent is presented. The surgery in all but three cases was intraocular.

2. In our hands, the proportion of drugs most successfully used consists of morphine sulfate (gr. 1/4), ephedrine sulfate (gr. 1/6), and scopolamine hydrobromide (gr. 1/200), dissolved under sterile conditions in 4 cc. of triple distilled water.

3. No case demonstrated morphine sensitivity or severe side effects. This series included a group of 26 patients over the age of 70 years.

4. It is imperative that the intravenous solution be administered slowly if side reactions are to be avoided.

5. The only established contraindication to the use of intravenous morphine includes all cases of allergic forms of bronchial asthma. It is not contraindicated in cardiac asthma.

6. Psychic sedation is obtained in 10 minutes by the intravenous route, while full analgesic action takes place in 20 minutes.

7. Amnesia of varying degrees is a prominent feature of this type of basal anesthesia.

Medical and Dental Building (1).

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VASCULAR NEVUS ASSOCIATED WITH HETEROCHROMIA

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The occurrence of nevus flammeus with heterochromia has rarely been reported. In those few case reports the lesions have been ipsolateral. Recent ophthalmic investigation[7,8] has tended to emphasize congenital predisposition, heredity, and genetic coupling to explain many of the freak ocular associations. It is with this in mind that an unusual twofold anomaly is herein presented.

In 1929, P. J. Waardenburg[6] reported four cases of nevus flammeus associated with glaucoma and heterochromia. In three cases, the hyperchromia was on the same side as the nevus flammeus and, in one case, the hyperchromia was on the opposite side. The report endeavored to show the relationship of the sympathetic heterochromia to glaucoma and that in turn to nevus flammeus. Both of these conditions are frequently mentioned or investigated in studies of primary and secondary glaucoma.

In 1935, Touraine, Solente, and others[4] reported a case of angiomato-encephalo-trigeminus associated with the status dysgraphicus. Although these authors have recorded several cases of dysgraphia in which heterochromia plays an important part,[1-3] no cases have been reported in which heterochromia, even though of the sympathetic type, has been shown in association with facial neurocutaneous dermatoses.

Touraine's patient, a 12-year-old boy, had a facial nevus of the flat type with involvement of the conjunctiva of the right eye, questionable involvement of the right retina, and a shadow in the parietal area of the skull suggestive of an intracranial angioma (von Hippel-Lindau's disease).

Besides these findings the patient had several features of the status dysgraphicus—coalescence of the eyebrows, overdevelopment of the middle incisors, small and caniniform lateral incisors, very pointed canines, and acrocyanosis.

The patient's body length was six inches less than his span and he had markedly flat feet. There were no neurologic manifestations of intracranial disturbance and no psychiatric disturbances.

The case was unique primarily because of the presence of some of the characteristic findings in the status dysgraphicus and their association with an angioma of the face. Since both conditions have been pointed out as being congenital anomalies, it is interesting to note their coëxistence in this individual.

In 1936, Stoll[5] reported a case of bilateral nevus flammeus associated with bilateral glaucoma in which it was mentioned that, as the glaucomatous condition progressed, hypochromia was present in each iris.

CASE REPORTS

CASE 1

History. The patient, a 32-year-old soldier, had no specific eye complaints. He was not aware of any difference in his vision. The involved right eye had never been red, painful, or photophobic. The patient knew of no inflammatory disturbance of this eye, and there was no history of trauma to this eye. The patient, who was a constant reader, had never been aware of any ocular disturbance or of any change in the condition of either eye.

At the age of 15 years he was struck in the region of the left malar prominence by a batted ball as he stepped from the school house onto the ball field. He was knocked over but did not lose consciousness. The left eyeball and left eyelids became discolored and remained so for five weeks. When the discoloration finally disappeared, a capillary network remained upon the cheek, forehead, and temple and has persisted ever since. The patient was certain that this vascularized area had not been present prior to this accident.

Family history. It was disclosed that the patient's mother had died at the age of 36 years from pulmonary tuberculosis. His father was alive and well, having no systemic or ocular involvements. There was one brother who did not have heterochromia nor any of the stigmas associated with the status dysgraphicus. His father, too, had no suggestion of the various skeletal and cutaneous signs associated with the sympathetic heterochromia symptom complex.

The patient's childhood diseases were of no moment as regards this case presentation since there was only the usual history of mild measles, infrequent tonsillitis, and a slight attack described as influenza.

Physical examination disclosed a fairly well-developed and well-nourished adult male who showed decided head tilt toward the right shoulder. There was an area of telangiectasia involving the left side of the face in the region of distribution

Fig. 1 (Rosen). *Case 1.* An area of telangiectasia involved the left side of the face in the region of distribution of the second and third branches of the trigeminal nerve.

of the second and third branches of the trigeminal nerve (fig. 1).

This was not a characteristic port-wine stain but resembled more closely the spider-web type of cutaneous lesion. There was no involvement of the lid or conjunctiva on this side. The nasal, oral, or buccal mucous membranes were not involved on either side. A very mild ptosis seemed to be present in the right eye which was light gray in color, while the left eye was a definite light-brown color. The pupils were equal in size and both reacted to light, to accommodation, and consensually, no difference being noted in the degree of reaction.

Slitlamp examination showed the cornea of the right eye to be studded with many crenated, greasy keratic precipitates which possessed elongated pseudopods. These keratic precipitates were present over the entire cornea as little gray masses in the center of which were some pigmented nuclear elements. There were some single pigmented spots throughout the substance of the endothelium.

The trabecular structure of the iris was definitely atrophic, as though its muscle element were becoming thinned and ironed out. The trabeculas looked as if the light could shine through very easily. The normal nodular structure of the inner circle of the iris had been replaced by a nonpigmented zone in which there was visible an occasional brownish, bulging nodule. Light shone readily through the pupillary border of the iris in many places, disclosing the atrophic nature of this portion of the iris.

On the anterior capsule of the lens there were many star- and triangular-shaped pigment masses which were arranged mostly in whorls over and within the pupillary zone. There were some thin, white, strandlike areas upon the capsule of the lens suggestive of areas of epithelial proliferation. The lens was clear from there to the region of the posterior cortex where three small white areas that resembled mashed potatoes were seen just off the nasal pupillary center. A polychromatic luster was obtained from the posterior capsule of the lens in the zone of specular reflection.

The vitreous was liquefied and degenerated, very little of the normal structure being visible. There was no abnormality of the fundus in the right eye.

Chest and heart. An area of telangiectasia was present on the patient's left anterior chest. There was no deformity of the sternum, scapula, breasts, or skeletal system. A suggestion of acrocyanosis was present but no intensification occurred upon exposure to cold.

There was no dyspnea or signs of pulmonary osteoarthropathy. There was no evidence of pulmonary edema. The trachea was in the midline; there were no abnormal pulsations in the neck. The chest was symmetrical; there was no retraction or bulging of the interspaces. The heart and great vessels were not abnormal in size; no thrills and no shock were observed. The heart sounds were of good quality.

Response to exercise was adequate. No murmurs were heard in left lateral portion after exertion. Carotid sinus response was zero. There was some evidence of mild bronchial asthma manifested by sibilant and sonorous rales in the right base and throughout the left lung. There was no impairment of resonance. Electrocardiograph report was negative.

The neurologic examination was essentially negative. Superficial and deep reflexes were not abnormal nor unequal. No pathologic reflexes were elicited. The neurologist had no further suggestions to offer regarding investigation of the original condition. Endocrinologic investigation was of no further aid.

Laboratory reports. Blood Wassermann and Kahn tests were negative. Urine was also essentially negative. Complete blood count was not abnormal in any respect. Repeated tests of sputum were negative for tuberculosis, eosinophiles, and Curschmann's spirals. The blood chemistry did not show any abnormality worthy of note. Basal metabolism rate was a +5. Sedimentation rate was 35; but, after two weeks, was 8; and after four weeks was 5. Mantoux test was negative to both first (0.0001 mg.) and second (0.001 mg.) dilutions.

The visual fields, blindspots, and intraocular tension (15 mm. Hg [Schiøtz] O.U.) were all well within limits regarded as normal.

The routine, ear, nose, and throat consultation did not uncover any visible mucous membrane dis-

turbance but a suspicious shadow in the left antrum led to an X-ray study of the sinuses. The report indicated involvement of this sinus but, when the left antrum was subsequently filled with a contrast medium, the X-ray statement was:

"The left antrum is well filled with contrast medium and shows evidence of thickened mucosa especially along its anterior wall." It was the opinion of the examining rhinologist that no angioma was present in the sinuses.

Comment. Case 1 is interesting because it presents a complicated type of heterochromia associated with a flat type of angioma of the face. Such a recorded observation may throw some light upon the theory of heterochromia by showing the possibility that it is congenital.

Case 2

History. This 23-year-old soldier had no physical or ocular complaints. The general physical examination was entirely negative. The only positive finding was a port-wine nevus flammeus involving the cutaneous area supplied by the three branches of the right facial nerve (fig. 2). This was a typical nevus flammeus which had apparently undergone no changes since birth. The tumor did not extend beyond the midline. There was no elevation of the nevus and no involvement of any of the mucous membranes other than the conjunctiva. There were no congenital anomalies elsewhere in the body.

Fig. 2 (Rosen). *Case 2.* A port-wine nevus flammeus involved the cutaneous area supplied by the three branches of the right facial nerve.

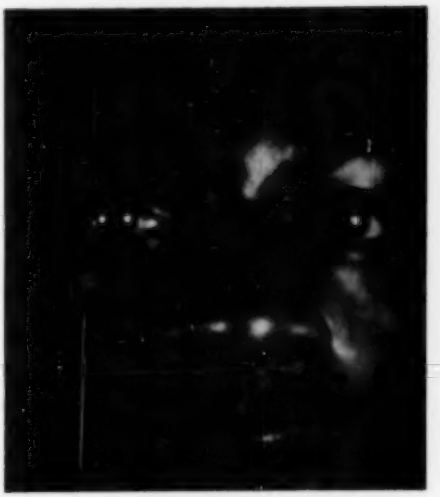

Fig. 3 (Rosen). *Case 3.* A nevus flammeus involved the entire left side of the face but did not extend beyond the midline.

Eye examination. Vision in each eye was found to be 20/20. The intraocular pressure was 23 mm. Hg (Schiøtz) in each eye. An area of telangiectasia was present in the entire upper half of the bulbar conjunctiva of the left eye. Under dilatation, the fundus showed no indication of a related vascular lesion. There was no rise in intraocular pressure following this pupillary dilatation.

In the right iris there was an area of brownish pigmentation occupying the nasal third of the iris and lodged in a field of greenish-blue iris.

Comment. This was evidently an example of heterochromia simplex associated with nevus flammeus and telangiectasia of the conjunctiva. Visual field studies, X-ray studies of the skull, and ear, nose, and throat investigations were all reported as negative. There was no evidence of telangiectasia or hemangiomas elsewhere.

Case 3

History. This Negro soldier, aged 32 years, was of rather short but stocky physique. It was readily apparent that his span (73 inches easily exceeded his height (65 inches) for his hands extended almost to his knees. He possessed several of the characteristics of the status dysgraphicus.

There was a suggestion of oxycephaly associated with winged scapulas and marked lordosis. There was no anomaly of the nipple pigmentation. The

Fig. 4 (Rosen). *Case 4.* A nevus flammeus on the left side of the face involved the entire region of distribution of the facial nerve.

knee and finger joints were hyperextensible. There were no anomalies of hands or feet.

A nevus flammeus involved the entire left side of the face but did not extend beyond the midline (fig. 3).

Eye examination. The left eye showed the heterochromia of typical melanosis oculi, with several round, purple-black deposits in the sclera and an iris which was much darker than its fellow. There was no indication of glaucoma as determined by tension, fields, or fundus examinations. The fundus of the left eye failed to show any suggestion of grouped pigmentation of the retina.

Comment. This case combined the features of the heterochromia of melanosis oculi with nevus flammeus and dysgraphia, and showed many of the findings of Case 1. There were no abnormalities of the teeth.

Case 4

History. This 28-year-old Negro soldier had no specific eye complaints. His physical examination was completely negative. No congenital anomalies were uncovered. A nevus flammeus was present upon the left side of his face involving the entire area of distribution of the facial nerve (fig. 4).

Eye examination. The iris on the left eye was a darker brown than that of his right eye. There were no keratic precipitates, no increase in intraocular pressure, no melanosis, and no telangiectasia. Family and childhood history were completely negative. The physical findings had been constant since birth.

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ASPERGILLOSIS OF THE CORNEA*

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Aspergillus infection of some part of the body is not infrequent and, although only rarely reported, is probably more prevalent than previously believed. The French and German literature, particularly, has numerous case reports of Aspergillus infections in humans. In the United States isolated instances of this infection have been recorded from time to time, most of them dealing with pulmonary involvement. Other sites of infection are the skin, mucous membranes of the conjunctiva and sinuses, and the external auditory canal.

Corneal infection by Aspergillus is comparatively rare, and was first reported by Leber in 1879. Since then, there have been several European cases recorded, and a few from this continent, most recent of which was that of Gifford in 1922. Other cases as mentioned by Sykes in his excellent review of Keratomycosis were those reported by Berliner (1882), Uhthoff and Axenfeld (1897), Schirmer (1896), Nobbe (1898), Wicherkiewicz (1900), Markow (1900), Karper (1903), Buchanon (1903), Johnson (1903), Marlin (1905), Zade (1907), Hayano (1918), Orlow (1913), Lindner (1913), Gruter (1914), Castroviejo and Urra (1921), and Fede (1930).

The genus Aspergillus belongs to the mycomycetes along with penicillium and verticillium, and is grouped under the true molds which are the most highly specialized forms of Hyphomycetes or fungi. Jacobson states that about 300 specimens of Aspergillus have been recognized and named, 60 of which are parasitic.

The parasitic members are sometimes found as harmless invaders of the respiratory tree and other parts of the body, but many become secondary invaders in inflammatory processes. These parasites are pathogenic to men, birds, domestic animals, and insects, the most susceptible animal being the pigeon. Consequently, Aspergillus infections are most commonly seen in pigeon and parrot breeders, grain handlers, house cleaners, and hair sorters, especially when there has been some preëxisting inflammatory or granulomatous process, for example, pulmonary tuberculosis.

The distribution and uses of Aspergillus offer an interesting and sometimes important hint of its presence. The saprophyte, A. niger, is often used in fermentation for the manufacture of citric and pyrogallic acids, and for fermenting soybeans; the spores of this black Aspergillus are common in dust or dirt. Other types of Aspergillus are often found on dead or dying plants, for example, on the bark of trees. There is a miscellaneous group which is present in the fingernails, joints, and on the skin. Aspergillus fumigatus is the most pathogenic and is found in the soil and dust from agricultural products. It is the only pathogen, among the Aspergilli, which has fulfilled Koch's postulates of disease transmission.

The manner of introduction of spores of Aspergillus fumigatus into the cornea is believed to be by a superficial injury. A raised, circular, gray plaque with crenated, rolled edges slowly begins to form on the cornea, accompanied later by hypopyon, congestion, and moderate pain.

According to many observers, the plaque consists of mycelial threads mixed with necrotic cornea and fibrin. Since this infiltration involves only the superficial layers in the early stages, the sequestrum, consisting of the whole fungus colony, may be removed

* From the Department of Ophthalmology, Veterans Administration Hospital, Hines, Illinois. Published with the permission of the chief medical director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed and the conclusions drawn by the authors. Presented before the Chicago Ophthalmological Society, May 16, 1949.

early and the cornea heals. If the deeper layers of the cornea are affected, the entire cornea may be lost, and the interior of the eye infiltrated, although this is rare (Schirmer, 1896; Castroviejo and Urra, 1921).

Diagnosis of corneal aspergillosis can be made by direct scraping and smear, and examination in sodium hydroxide solution. Culture on Sabouraud's medium is of value. Within 24 to 72 hours, there will appear white, round points, which tend to coalesce and adhere to the medium. The particular species cultured will determine the color of the growth. Aspergillus fumigatus assumes a greenish color at first and, after 10 to 12 days, becomes smoky. The culture is smooth, wrinkled, or forms concentric rings, depending upon the species cultured.

Treatment, as recommended by some European authors, consists of removal of the corneal slough, cauterization of the affected area with galvanocautery, and administration of large doses of potassium iodide systemically and locally. A dense leukoma usually results. Paracentesis or delimiting keratotomy is not advised; Wurdemann recommends a watchful expectancy for the regressive phase, and abstention from early surgical intervention.

Case report

History. On December 17, 1947, S. G., a 57-year-old white man, entered the Veterans Administration Hospital at Hines, Illinois, with complaints of anorexia, weight loss, chronic cough, and back pain of many months' duration, and pain in the left eye for one month. He had been a tree trimmer for over 10 years until 1941, when he developed a chronic cough.

On the basis of a chest X-ray study, he was hospitalized at the Veterans Administration Hospital at Wood, Wisconsin, for pulmonary tuberculosis. During a two-year hospitalization there, he had two marked pulmonary hemorrhages and frequent-blood-streaked sputum; however, his general vigor remained good. Following the occurrence of pain in the thoracolumbar region, a diagnosis of tuberculous spondylitis was made. He was later discharged as an arrested case of pulmonary tuberculosis. Records of sputum examinations done at that time are not available at present.

From 1943 to 1946, there was some weight loss due to poor living conditions. In 1946, he was admitted to the Veterans Administration Hospital at Hines and an arthroplasty was performed for a fracture of the left hip. At that time, numerous sputum examinations were negative for tubercle bacilli.

At the present admission, the general physical examination revealed moderate emaciation, slight liver enlargement, and rales in the right upper lobe of the lungs. Laboratory findings were normal, except for sedimentation rate of 31 mm. per hour. Thirteen subsequent sputum smears and cultures revealed one smear containing many acid-fast bacilli. X-ray studies of the chest on December 19, 1947, showed scattered fibrocalcific infiltrations in the upper half of both lungs. Advanced pulmonary tuberculosis, portal cirrhosis, and malnutrition were the tentative diagnoses.

Ocular examination. On December 18, 1947, the patient was presented to the eye clinic with complaints of pain and decreased vision, left eye, of one-month duration. Examination of the eyes revealed vision of: R.E., 20/50, correctible to 20/30; L.E., hand motion at four feet, not correctible. Right eye was completely negative externally and internally, except for some mild posterior, lenticular, cortical sclerosis.

Examination of the left eye revealed moderate lid edema and mixed bulbar conjunctival injection. There was diffuse corneal edema. An erosion of the cornea, nasally, about 4 mm. in diameter, extended down to the midstroma. The ulcer had rigid edges, and a dirty gray base was present. This excavation stained with one-percent fluorescein. A hypopyon of about 2 mm. in depth was evident in the anterior chamber.

The iris was normal. The pupil was 5 mm.

in diameter and reacted to light and accommodation. The lens was normal. The fundus could not be visualized readily because of the corneal edema. Extraocular movements and tactile tension were normal, bilaterally.

A tentative diagnosis of acute, serpiginous ulcer with hypopyon of the left eye was made. Scrapings were taken for smear and culture from the conjunctiva and ulcer of this eye.

The patient was placed on two-percent atropine (one drop, three times daily) and hot wet dressings, locally, to the left eye. He was also given subconjunctival penicillin injections, consisting of 50,000 units of penicillin dissolved in equal parts of 1:1,000 adrenalin and one-percent novocain, to make a total volume of 0.5 cc. per injection (Sorsby). Three subconjunctival injections were given each day to the left eye. He was also given 40,000 units of penicillin intramuscularly every three hours, and 5,000 units penicillin per cc. of saline, one drop every three hours, locally to this eye.

On December 20, 1947, a bacteriologic report from the previous smear and culture from the left eye revealed Gram-positive diphtheroids and a coagulase-positive hemolytic Staphylococcus aureus. No inclusion bodies or acid-fast organisms were found.

After 48 hours of this treatment, the patient was asymptomatic. He had received a total of 10 subconjunctival penicillin injections, and had been given intramuscular penicillin with penicillin drops and atropine, locally. On December 24th, the edges of the ulcer showed epithelization, and the diameter of the excavation had decreased to 2 mm. The hypopyon had completely disappeared. The conjunctiva exhibited a peculiar reddish-yellow discoloration with a tendency to adhere to the globe. This was later attributed to the subconjunctival injections, which were somewhat painful in spite of the inclusion of one-percent novocain in the solution. The patient was then started on penicillin ointment, 100,000 units per gm. in one part of mineral oil to nine parts vaseline, locally to the left eye, and was seen daily in the eye clinic.

Course. On December 26th, a small hypopyon began to reform and continued to increase, although the 2-mm. ulcer remained unchanged in size and configuration. Paracentesis of the cornea was performed on December 30th and the anterior chamber was irrigated with 0.4-percent saline. The wound was re-opened the following day; the patient continued to receive atropine, hot wet dressings, and penicillin ointment locally. He was again put on subconjunctival penicillin injections, every six hours, three times daily. However, since the hypopyon continued to reform, the subconjunctival injections were stopped.

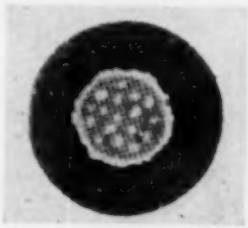

Fig. 1 (Stern and Kulvin). Aspergillosis of the cornea (after Wicherkiewicz). Reprinted with permission from Duke-Elder, W. S.: *Textbook of Ophthalmology.*

Subsequent treatment with sulfonamides locally and further paracentesis were not beneficial, and the ulcer assumed a chronic appearance. On January 30, 1948, the ulcer was yellow-green in color with multiple, discrete, calcareouslike infiltrations at the base and rim, resembling an illustration by Wicherkiewicz (fig. 1). Unfortunately, an actual photograph of the patient's eye was not obtained. There was a surrounding, circular, superficial infiltration of the cornea.

Supportive therapy to the eye was continued and, on March 22nd, the vision was 3/400. In the cornea, there was a centrally located grayish crater which now measured about 5 mm. in diameter. All stromal layers beneath the plaque showed infiltration, and the mild aqueous flare was accompanied by a small hypopyon. Penicillin drops 2,000 units

Fig. 2 (Stern and Kulvin). Culture plate showing growth of Aspergillus fumigatus. The culture was from the plaque removed from the patient's cornea.

per cc., were again tried locally, together with intramuscular penicillin and paracentesis, but this was of no value.

On March 29th, there was a suspicion that

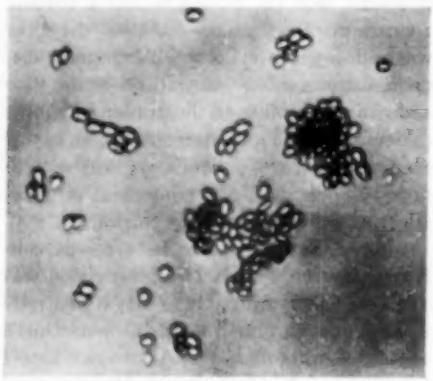

Fig. 3 (Stern and Kulvin). Microphotograph (×500) of the conidia or spores of Aspergillus fumigatus.

patient might have a fungus infection, possibly Aspergillus, and, on March 30th surgical removal of the plaque from the cornea was performed. This plaque was cultured for fungi. Aqueous was also withdrawn and culture made for bacteria and fungi. The site of the ulcer was cauterized with 10-percent trichloracetic acid and neutralized with 70-percent alcohol. The paracentesis wound was re-opened for five successive days.

A bacteriology report revealed no organisms found on smear and culture from the aqueous; however, culture made directly from the cornea revealed a hemolytic Staphylococcus albus. Culture for tuberculosis was

Fig. 4 (Stern and Kulvin). Corneal infiltration and opacification of the left eye of patient, S. G. This picture was taken on May 6, 1948.

negative. An April 9th, it was reported that Aspergillus fumigatus was cultured from the plaque which was removed from the cornea (figs. 2 and 3).

The patient was then placed on local iodine therapy (five gr. of potassium iodide with five minims of Lugol's solution per ounce of distilled water). He was also started on high vitamin intake of vitamins A, B complex, C, and D, and one-percent atropine was continued locally to the eye.

On April 12th the patient had a slight flare in the aqueous, and there was some old pigment present on the anterior lens capsule. Dionin powder was applied locally to the cornea.

The cornea continued to show a clearing of the central area and, on April 20th, there was some residual infiltration of the cornea

in the nasal half (fig. 4). The aqueous was clear. The central corneal opacification continued to clear, and visual acuity increased to 20/200, not correctible. The corneal condition seemed to have reached a stationary stage. There was a leukoma, centrally located, with a diameter of about 6 mm. Vision at time of disposition was 20/200.

Discussion

The source of the infection and its response to medication in this case present interesting considerations. The patient's occupation as a tree trimmer offers a possible clue to the source of the pulmonary and corneal infections. The frequency of blood-streaked sputum in the absence of debilitation is characteristic of pulmonary aspergillosis; the chest X-ray film (fig. 5) showed atheromatous lesions throughout the arterial tree of the lungs, another point of differentiation from pulmonary tuberculosis (Jacobson). Likewise, only one from many sputum examinations was positive for tuberculosis, and the frequent coexistence of pulmonary tuberculosis and aspergillosis is well known; which infection was primary is problematical.

In later sputum examinations for fungi, following establishment of the corneal diagnosis, no fungi or tubercle bacilli could be found. Bronchoscopy and direct culture was considered, but not performed because of the patient's age and only recent recovery from pulmonary activity. Thus, the pulmonary diagnosis was still indefinite but important in respect to the use of systemic iodine therapy.

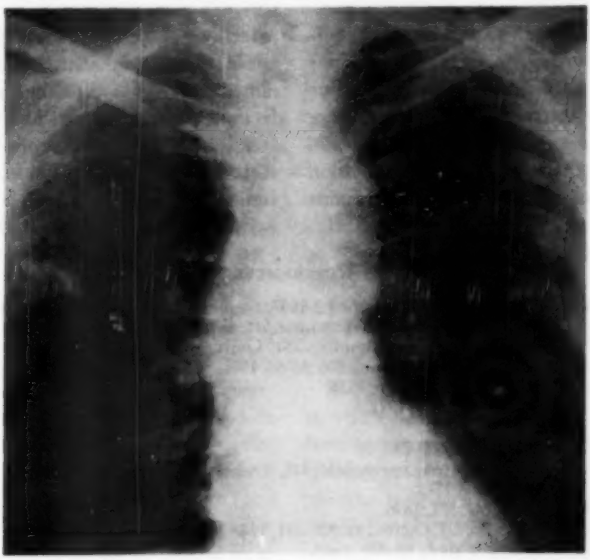

Fig. 5 (Stern and Kulvin). Atheromatous lesions may be seen throughout the pulmonary tree.

The possibility of the corneal infection being due to contamination and secondary invasion by Aspergillus must be considered. The original offending organisms cultured from the cornea were Gram-positive diphtheroids and a coagulase-positive hemolytic Staphylococcus aureus. There was immediate good response to local and general penicillin therapy, which would not be expected in a

primary mold infection. Aspergillus could have been introduced during the subconjunctival injections, although completely sterile technique and solutions were used. That the mold was present later was borne out by the poor response to penicillin, the positive culture, and the excellent reaction to local iodine therapy. Most cases of fungus infection give a history of trauma by some earthy or vegetable material, which presumably carries the fungus (Bedell; Wright). Fazakas states that fungi are present in 25.65 percent of normal eyes and 37 percent of diseased eyes.

The question of the relationship of Aspergillus and other fungi to the various lesions in which they have been found by various observers remains unsettled. Their presence alone does not signify cause and effect, and the problem of their activity in combination with that of bacteria is one that yet remains unanswered.

Summary

Aspergillus, a true mold, is a rare invader of the cornea, usually introduced by a superficial injury. The lesion is a gray, circular plaque with rolled edges, associated with moderate pain, congestion, and hypopyon. The sequestrum formed may be removed surgically, and the remaining infection treated with iodides. Perforation of the eye is rare. Diagnosis is made by smear and culture on a special medium (Sabouraud's).

A case is presented, illustrating a possible relationship of the corneal infection to the patient's previous occupation and pulmonary infection. The characteristic poor response to antibiotics, and the usual excellent results obtained with local iodine therapy in fungus infections is demonstrated. The presence of fungi in the cornea is often incidental or secondary to other infection, but it may assume a primary role.

Veterans Administration Hospital.

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NOTES, CASES, INSTRUMENTS

SARCOIDOSIS*

REPORT OF CASE MANIFESTED BY RETROBULBAR MASS, PROPTOSIS, DESTRUCTION OF ORBIT, AND INFILTRATION OF PARANASAL SINUSES

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Sarcoidosis can be defined as a chronic, indolent, and benign infectious disease of unknown cause.[1] The diagnosis is usually made by: (1) The exclusion of tuberculosis and other infectious diseases, including a negative skin test for tuberculosis; (2) appearance of eosinophilia, increase in erythrocyte sedimentation rate, and increase in serum proteins with reversal of A/G ratio; (3) lymph-node biopsy which often reveals the sarcoid changes; (4) biopsy of the lesions demonstrating the characteristic microscopic picture.

The microscopic slide shows the lesion to be composed of many small tubercles which are made up of large pale epithelioid cells, small lymphocytes, and giant cells often containing peculiar basophilic inclusion bodies (Schaumann bodies). There is practically never any central necrosis and caseation does not occur in the uncomplicated case.

It is true, however, that in many cases the pathologist is unable to make an unequivocal diagnosis of sarcoidosis from the microscopic slide, and the diagnosis is made only by correlating the clinical features with the microscopic findings.

Longscope states that: "One is impressed by the fact that symptoms, when they exist, are caused primarily by the mechanical interference with the function of the organs rather than by any form of intoxication. When the miliary 'hard tubercles' or sarcoids collect in great numbers, they tend to displace or destroy normal tissues or may even produce tumorlike masses that involve one or several organs."[2]

Practically every organ and system of the body has been reported as being affected by this disease. Especially common locations have been lymph nodes, lungs, skin, bones, and eyes. Although Levitt[3] reviewed 100 cases of sarcoidosis and found eye involvement in 43 cases, he did not report any with involvement of the orbit; nor does Freiman[4] in his recent comprehensive review of the literature.

Reis and Rothfeld,[5] in 1931, described a case in which there was bilateral exophthalmos. Autopsy showed a flat, translucent, yellowish, hard infiltration around the infundibulum, chiasm, optic nerves, and extending back to the cerebral peduncles.

In 1939 King[6] reported what he believed to be the first case of sarcoid tumor mass of the orbit. From a patient who complained of a lump under the lower lid of the eye, he excised a smooth fleshy tumor mass in the orbital fat beneath the eyeball.

Kaplan,[7] in 1948, described a sarcoid case in which he removed a yellowish, indurated, cartilagenouslike mass in the retrobulbar space from a patient who complained of a painless bulging of the upper lid. In 1942, Bordley and Proctor[8] described a case of sarcoid in which the characteristic granuloma was found in the paranasal sinuses.

Certainly sarcoidosis of the orbit or of the nasal sinuses is rare. We wish to report a unique case of sarcoidosis in which there was unilateral proptosis, destruction of part of the orbit, and infiltration into the paranasal sinuses by direct extension from a retrobulbar sarcoid granuloma.

CASE REPORT

History. The patient, a 36-year-old Negro cotton picker, was first admitted to the John Sealy Hospital in October, 1945. He com-

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Fig. 1 (Rider and Dodson). Appearance of the left eye, December, 1945.

plained of a blind painful protruding left eye. The onset of symptoms began in 1940 as a sharp aching pain in the left temporal region. Shortly after the onset the pain became constant and dull in character and persisted to his admission. In 1941 he developed a deep-seated retrobulbar constant aching pain which also persisted.

A few weeks after this began he experienced occasional transitory diplopia and was told by his friends that his left eye was increasing in size and becoming more prominent. During the time from 1942 to 1945 the left eye continued to slowly increase in size and prominence, and coincident with this was a progressive loss of vision until there was just bare light perception left. The right eye was unaffected.

Physical examination. A complete physical examination was normal except for the left eye. Bare light perception was present. There was moderate proptosis, but no chemosis or pulsations were noted. There was a primary type of optic atrophy. The vessel pattern was not disturbed. A hard, firmly attached mass was felt occupying the lower part of the left orbit.

Laboratory examinations. Urinalysis, serologic test for syphilis, serum for glanders, tuberculin skin test (O.T.—1:1,000) were all negative. The blood counts were normal except for a 9-percent eosinophilia.

X-ray studies. The chest showed a slight generalized increase in density of all peripheral lung fields. The paranasal sinuses showed destruction of the mesial portion of the left sphenoid ridge and fissure. The left frontal, ethmoid, and maxillary sinuses were cloudy.

Surgery. Exploration of the left orbit revealed a hard tumor mass below the globe which extended posteriorly beneath the eyeball. Radical maxillary sinusotomy revealed a mucous membrane which was thickened and fibrotic. Biopsy of the orbital mass and sinus membrane revealed a nonspecific type of granulomatous tissue containing giant cells when studied microscopically.

After six weeks of completely afebrile, uneventful hospitalization, he was discharged.

On readmission in October, 1947, he stated that the vision in the left eye was completely lost and that the retrobulbar pain was still present. Marital, family, and past medical history were irrelevant. Although he had never had chills, night sweats, or fever, a systemic review revealed that he had recurring mild episodes of "wheezing" at irregular intervals.

Physical examination. A general physical examination was again normal except for a few small, scattered, discrete, firm, freely movable, nontender lymph nodes in the anterior and posterior cervical chain. A few similar nodes were noted in the epitrochlear regions bilaterally. The liver was just palpable beneath the costochondral margin on deep inspiration. There had been no weight loss.

The left eye revealed marked proptosis—the exophthalmometer reading was 29 mm. The eye was turned out, down, and was fixed. There was marked chemosis of the bulbar conjunctiva and the cornea had a central perforation with prolapsed uveal and lens material. A firm nonmovable, nontender, orbital mass was felt in all quadrants of the orbit except for the upper temporal. This had obviously increased in size since the last observation. There was no light perception. The lids were unable to close over the eye.

Laboratory examinations. Urinalysis, serologic test for syphilis, stool examinations for ova, parasites, and culture, blood phosphorus, alkaline phosphatase, plasma proteins,

repeated sputum examinations, and bronchoscopic aspirations for acid-fast bacilli and fungi, tuberculin skin test (O.T.—1:100), coccidiodin skin test (1:100), and electrocardiogram were all either negative or normal. Although blood counts were normal, there was a 14-percent eosinophilia. The sedimentation rate varied between 18 and 30 mm. per hour (Wintrobe method). The blood calcium was 11.5 mg. percent. Two spinal fluid examinations revealed negative Wassermann but a protein that varied from 48 to 68 mg. percent. The Lange curve was in each case a first zone type; that is: 44,211,100 and 54,431,100.

X-ray studies. The hands and feet revealed no abnormalities. The skull showed an extension of the destructive process in the left orbit. The superior orbital fissure and optic foramen were no longer visible. The sphenoid ridge showed further destructions. There was an increased infiltration of the left maxillary antrum with dense clouding of the sphenoid sinuses. Reëxamination of the chest showed an extension of the inflammatory process previously present, as well as a fibro-exudative infiltration involving the upper half of both lung fields which was reported as suggestive of sarcoidosis.

Biopsy of epitrochlear nodes showed only nonspecific inflammatory changes.

On November 1, 1947, an enucleation of the left eyeball was accomplished. After removal of the globe, the orbital tumor mass was found to occupy practically the entire orbital space. It was firmly attached to the floor, medial, and lateral orbital walls. It was cartilagenous in character and yellowish white in color. A biopsy was taken and during this procedure there was minimal bleeding. Tissue culture of the orbital mass was negative for pathologic organisms.

Microscopic examinations. Sections of the enucleated eye revealed no sarcoid changes. Sections of the orbital tumor were reported as being suggestive of and probably representing sarcoidosis, especially in view of the clinical features. These same sections were reviewed by two other pathologists and their findings also supported the diagnosis of sarcoidosis.

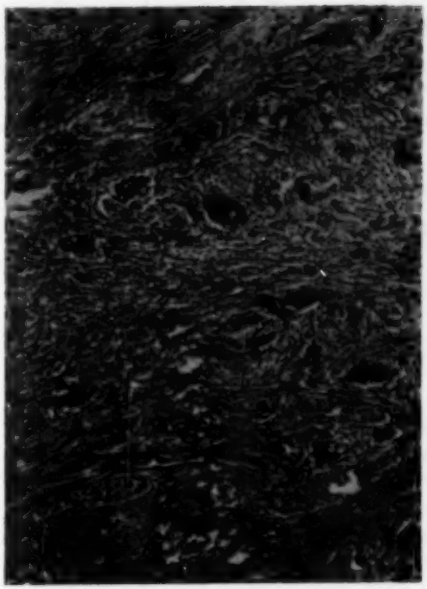

Fig. 2 (Rider and Dodson). A photomicrograph of a section of the tumor tissue.

Summary

A rare case of sarcoidosis has been reported in which the granulomatous lesion was found to form a retrobulbar mass which caused destruction of the orbit, resulted in severe proptosis with total loss of vision, and infiltrated into the paranasal sinuses. The diagnosis was made by correlating the clinical features—increased eosinophile count, increased sedimentation rate, pulmonary changes, exclusion of tuberculosis and other infectious diseases, and chronic benign course—with the microscopic examinations.

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A MAGNETIC PERIMETRY SET*

MORGAN B. RAIFORD, M.D.
Atlanta, Georgia

To facilitate the technique of taking tangent and peripheral visual fields, a set of test objects having a magnetic principle† was developed. The test objects are constructed of plastic material with a metal back giving the size in millimeters. Each size number is pigmented to denote the color of the object. The colors are white, blue, red, and green, each with standard Heidelberg pigments. The test objects are in the following sizes: 1, 2, 3, 5, 10, 15, and 20-mm. in white, blue, red, and green, with a 0.5 mm. in white.

Fig. 1 (Raiford). A magnetic perimetry set.

The wand has a small magnet at the tip and is made into two sections so as to fit in the perimetry set case. Each series of colors has a row of snug-fitting depressions to hold the different sized test objects. At the beginning of each row, a small indentation is colored to correspond to the test objects belonging in that row.

A section is provided for charting pins and occluders (fig. 1). The perimetry case is constructed of plastic material with a flat, tight-fitting top, which prevents any displacement of the test objects.

The test objects have the advantage of ease of selection by the perimetrist. The small magnet at the tip of the wand holds the test objects firm and has proved most efficient in a series of over 1,700 cases tested for fields by this technique.

The test objects are not touched by the examiner at any time during the taking of visual fields. By being placed face down when not in use, the colors are not affected by dust or fading.

Since the test objects are thin, as is the magnet, their contours do not create any shadow effects upon the tangent screen or the perimeter. The wand and nonpigmented portions of the test objects are black like the background of the perimeter or tangent screen, so contrast is absent. The colors, being flat, do not produce any highlights or reflection.

Grady Clay Memorial Clinic,
Emory University.

* Manufactured by J. E. Limeburner and Company, 1923 Chestnut Street, Philadelphia, Pennsylvania.

† The use of the magnetic principle in the taking of visual fields was introduced in the Wesseley Clinic, Munich, Germany, in 1923. (Vail, D.: Personal Communication.)

CONCEALED GLARE FILTERS OR SUPPLEMENTARY LENSES*

EMANUEL KRIMSKY, M.D.
Brooklyn, New York

The broad temples of the newer type zylonite frames make it possible to attach accessory lenses or filters which can be concealed or countersunk against the outer walls of these temples (fig. 1).

For the first model, a tycoon type of zylonite frame was selected in which the temples were at the same levels as the visual axes. A 30-gauge, green-colored plastic was arbitrarily selected and cut to the width of the temple bar; its length was sufficient to cover the transverse diameter of the lens mount. Two pieces were prepared, one for each eye.

A jointed bracket was screwed into the anterior part of each temple bar, and the strips of plastic were then screwed into the respective bracket supports. The glare filters could thereby be replaced by other filters or by supplementary lenses. Each plastic filter could be rotated away from its temple bar and brought forward to rest on the permanent or wearing lens (fig. 2).

Cosmetically, a strip of glare filter would appear unconventional and would raise the question as to whether it could possibly have antiglare value. From a functional standpoint, however, a width of filter sufficient to cover the cornea was found adequate for protection. Moreover, the subject by tilting the head slightly forward or backward could bring his pupils above or below the protective strip of filter and thereby avail himself of unhampered vision when desired (fig. 3).

With proper arrangement of temple bars in relation to viewing frame proper, it should be possible to provide lens coverage over a higher or lower area of lens frame. One may find it convenient to slip over distance glasses a pair of bifocal or other accessory lenses made either of plastic or of glass; or one may widen the temple bar just behind the lens frame to hold both a glare filter as well as accessory lens. As a bifocal accessory lens system the advantages of this design are obvious in so far as the subject is relieved from the often difficult situation of having to walk around with bifocal lenses to blur distant vision in the lower visual field.

The originality of this device lies in the utilization of the wide temple bar to provide a concealed means of holding either or both a glare filter and supplementary lens; also, in recommending in the interests of functional design the practical use of narrow strips of glare filter.

745 Eastern Parkway (13).

Fig. 1 (Krimsky). Glare filters concealed against outer walls of temples.

Fig. 2 (Krimsky). Glare-filter strips covering corneas.

Fig. 3 (Krimsky). Looking over filters by slight tilt of head.

* Presented at the meeting of the American Academy of Ophthalmology and Otolaryngology, Chicago, October, 1948.

SOCIETY PROCEEDINGS

Edited by DONALD J. LYLE, M.D.

COLLEGE OF PHYSICIANS OF PHILADELPHIA

SECTION ON OPHTHALMOLOGY

January 20, 1949

DR. PERCE DELONG, *chairman*

ABDUCENS PARALYSIS IN BRUCELLOSIS

DR. JOSEPH C. YASKIN AND DR. RUSSELL S. BOLES presented this paper. While abducens paralysis is a common occurrence and is usually due to causes that are readily ascertainable, one occasionally encounters isolated external rectus palsy for which there is no etiologic diagnosis. The idiopathic abducens palsy is as rare as Bell's palsy is common. The diagnosis cannot be established until the patient makes a complete recovery. Two cases of isolated abducens palsy due to brucellosis are reported. In both cases the agglutination tests were positive. In the first case the abducens palsy appeared several months after the acute stage of a severe infection manifested by chills, fever, sweats, mild meningeal irritation, and delirium. In the second case the abducens palsy appeared 10 days after an attack of headache, nausea, and backache. Both patients made a complete recovery.

Undulant fever in its various forms is known to attack the nervous system—causing meningitis, meningo-encephalitis, and meningomyelitis, and occasionally neuritis of the cranial nerves. It is believed that our two cases were due to brucellosis infection.

It is suggested that among other causes of abducens paralysis one should consider the existence of latent brucellosis.

Discussion. DR. RUSSELL S. BOLES: It is a great pleasure for me to have an opportunity to discuss this condition. As far as I can understand, paralysis of the sixth nerve is not altogether an ucommon disorder. These two cases are unique in that they appear to be due to brucellosis. This is a disease that exhibits no particularly specific lesions, but, as in the case of most general nonspecific infections, it may affect various organs in a purely nonspecific way.

The three species of organism causing brucellosis or undulant fever are the Brucella abortus, Br. suis, and Br. melitensis. In the two cases reported, I do not think Dr. Yaskin or I can claim any credit for suspecting a relationship between the paralysis of the sixth nerve and the infection. In the second case, which happened to be one in my private practice, I had no suspicion whatever of undulant fever being present as a cause of the paralysis. I did the agglutination tests simply because of the man's severe occipital headache and backache, profuse sweats, malaise, and indisposition.

Brucellosis, as I said, exhibits no particularly significant lesions, but is very protean in its manifestations, providing the various symptoms that I have described. In the first case, one of the undulant variety, the sixth-nerve palsy did not develop for almost a year after the onset of symptoms, while in the second case it developed in 10 days. The former was a chronic type of the disease; the latter, acute. I think it is important to remember that the disease may be acute as well as chronic, although it is seldom recognized in its acute stages. The diagnosis of brucellosis may be made on the symptoms and laboratory findings. Blood cultures are positive in about 25 percent of cases. The blood agglutination tests are positive in a high titer in most cases. Both may vary, however, during the course of the disease.

The complications of brucellosis are quite varied. Arthritis is a common complication. Meningitis, as far as I have been able to gather, is not too frequent, although I believe Dr. Yaskin found—in a survey of neurologic literature—that it was not an unusual complication. Pericarditis and subacute bacterial endocarditis occur. Uveitis is fre-

quently seen in epidemic areas. The complication of unilateral sixth-nerve palsy I am sure is very unusual.

DR. JOSEPH C. YASKIN: I do not believe that I have anything to add except to emphasize that whenever we cannot find a satisfactory cause for a lateral mucle paralysis, it is best not to call it idiopathic. Most cases of isolated abducens palsy eventually turn out to be associated with widespread involvement of the nervous system. In the present presentation we call attention to brucellosis. In the future, other infections or intoxications may prove to be the cause of abducens palsy. It is well to keep our minds open before labelling a given case as idiopathic.

SENSITIVITY TO GOLD BALL ORBITAL IMPLANT

DR. H. WALTER FORSTER, JR. (by invitation) AND DR. ROBERT F. DICKEY (by invitation) reported a patient who showed a marked sensitivity to a 14-karat gold ball both clinically and by patch test. This had been implanted into her left orbit at the time of enucleation five years before the onset of symptoms. No such case has previously been reported in the literature. The paper was published in full in this JOURNAL, volume 32, page 659, May, 1949.

CONGENITAL INTERNUCLEAR REFLEX

DR. EDMUND B. SPAETH presented two cases to illustrate the possibility of an association which exists as an internuclear reflex between the nuclei of the sixth and third nerves. In the presentation, the author considered further the possibilities of these cases; that is, congenital associated movements, as to the anatomic position for their development. This included further consideration of the cause of the Marcus Gunn associated movements as well as the other various oculomotor associated movements.

Discussion. DR. JOSEPH C. YASKIN: My contribution to this paper will consist of two parts, of which the first is the more important.

This first part is a confession of ignorance which is not intended to belittle Dr. Spaeth's contribution. I am and have been for years bewildered by the neurology of the extraocular muscles, and especially the abnormalities for which we have no proven anatomic basis.

Dr. Spaeth quoted Tinley, Riley, and Bing. Dr. Tinley and Dr. Riley wrote a magnificent book on the structure and function of the nervous system, and Dr. Riley has written some valuable monographs on the extraocular muscles. Dr. Bing is a superb clinician still practicing in Switzerland.

These authors have made many statements regarding the anatomic connections between the various extraocular nuclei and nerves, but to the best of my knowledge there is still a lack of microscopic verification of these statements.

We learn a great deal by inference and from comparative anatomy and embryology. Most of it, however, remains inference and, because of the abstract nature of the material, I am not altogether clear in my mind about a great many phenomena. From a practical standpoint, and for many years, I have been trying to find out why the extraocular muscles escape in pseudobulbar palsy, in which most of the bilaterally innervated muscles of the head are involved. I have found no satisfactory explanation for this phenomenon either in standard textbooks or reference books, or in discussions of men like the late Dr. William G. Spiller, and Dr. Otto Marburg, who was my teacher of anatomy at the Neurological Institute of Vienna. I have spent many hours with Dr. Marburg trying to unravel the various connections of the extraocular nerve nuclei in the posterior longitudinal bundle, but could find no satisfactory answer to a good many questions.

All that I have said does not detract from the labor that Dr. Spaeth gave in preparing this presentation. It is quite possible that having become absorbed in the subject, he sees a great deal more in it than most of us can. For instance, he is much more familiar with the embryology of the various structures than most of us are. There can be no question about the validity of his observa-

tions. His interpretations appear to be sound in the light of the knowledge that he has on the subject at the present time. Lastly, the practical value of recognizing these various syndromes is important since they will lead to a better therapeutic approach.

M. Luther Kauffman,
Clerk.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

January 19, 1949

Dr. John E. Rice, *presiding*

Antiglaucoma drugs

Dr. W. Morton Grant of Boston said that, from the inception of effective medical treatment of glaucoma in 1876 to the present time, a review of the literature reveals that the antiglaucoma activity of only approximately, 35 compounds has been investigated clinically or experimentally, although several times this number of potentially active substances have been available in the laboratory. Of the compounds investigated clinically, those which have best stood the test of time come from the categories of parasympathomimetic and sympathomimetic substances, while sympatholytic substances until recently have not proved particularly effective.

Concepts of the mode of intraocular-pressure control by these various drugs appear to be based largely on clinically apparent mechanical factors concerning the iris and ciliary muscles and to a smaller extent on experimental observations of supposed vascular factors in animals. Little correlation has as yet been made with current concepts of the physiology of aqueous-humor formation.

In connection with mechanical factors, it is suggested that possibly greater attention should be given the cyclotonic actions of miotic drugs. This viewpoint is supported by preliminary observations in 17 glaucomatous patients employing a compound, 2268F which resembles natural muscarine in having a considerable stimulatory effect on the ciliary muscle, and which was unusually effective in lowering the tension in a number of eyes where the iris could not have been very effective due to atrophy, mutilation, and so forth.

Regarding the elucidation of nonmechanical factors in tension control, little attempt appears to have been made to interpret available experimental and clinical information on the increased leakage of large molecules from blood to aqueous which is observed in various phases of action of both parasympathomimetic and sympathomimetic substances. In the light of recent developments in the knowledge of aqueous-humor formation which have led to the secretion-diffusion hypothesis of Kinsey and Grant, it may be postulated that increased permeability of the blood-aqueous barrier impairs the osmotic efficiency of this barrier and tends to lower intraocular pressure by permitting secreted electrolytes to leak prematurely back to the blood. However, in the parasympathomimetic category of drugs there is at present no correlation of antiglaucoma effectivity with intensity of effect on the barrier. Also, there appears experimentally and clinically to be a rapid development of tolerance by the barrier to the action of these drugs.

In the special subgroup of cholinesterase inhibitors, those which have been investigated to date clinically appear to have a common fundamental pattern of muscular, vascular, and probably barrier action, with acetylcholine preservation as the common denominator, and to vary only with regard to duration of action, tendency to produce sensitization, and so forth.

In the sympathomimetic category, information is available on the relative antiglaucoma activity, vascular and blood-aqueous barrier effects of only a single compound so that the relative significance of these factors remains uncertain.

In the category of sympatholytic substances, of which dibenamine is reported to be among the most active, more antiglaucoma action is apparently achieved than previously

obtained by sympathectomy. The action may, therefore, be attributable to antagonism of the hormonal participation of epinephrine in the Friedenwald redox secretory mechanism rather than to blocking of sympathetic innervation, although the possibility of other simpler effects on the barrier remains unsettled.

Discussion. Dr. William Beetham: I thought you would like to have some up-to-the-minute data on the latest drug, dibenamine. Correct me if I'm wrong, but I think this is the first time it has been used in Boston. It is a research drug, as Dr. Grant pointed out. It is very toxic, and has only been administered intravenously. Forty-eight hours ago, the golden moment arrived. The patient was an elderly lady, 79, whom I had operated upon four years ago because of neglected acute glaucoma in one eye. This responded to an iridectomy very nicely, and she has had wonderful pressure in it ever since, but only shadows in the temporal field. Because the anterior chamber in the good eye was so shallow, I put her on 2-percent pilocarpine, used 2 or 3 times a day. I have seen her at intervals every four months from that time. The last time was six weeks ago. She had 20/30 vision, full field, normal disc, and tension of 19 mm. Hg (Schiøtz).

Forty-eight hours ago, she telephoned me with the story that, while she was playing bridge in the afternoon, she had had sudden pain and blurred vision in the good eye, headache, and nausea. I thought I knew what had happened. I told her to put the drops in every hour during the night and get into bed, and to come into the office in the morning.

She came in, and the tension was 90 mm. Hg (Schiøtz). She was very sick, so I sent her to the hospital, and then went about trying to get medical approval for giving dibenamine. That wasn't easy because the medical man didn't know about it, and he wasn't keen about using some drug he didn't know about. But during the day, he found out about it, and gave his approval.

The tension was 90 mm. Hg at 9 a.m.; it was 100 mm. Hg at 4 p.m. The patient had been on 4-percent pilocarpine and eserine just about as often as the nurse could put it in. At seven o'clock last evening, dibenamine was given intravenously. It is supposed to be given quite slowly, and she had a pretty reasonable night.

At eight o'clock this morning, the tension was 30 mm. Hg and the cornea was clear. She had had, from the time I first saw her, complete miosis; the pupil was no more than 2 mm. at the most, and she had an almost obliterated anterior chamber, so that I was really puzzled as to what I was going to do if this didn't work. But, at eight o'clock this morning, the tension was 30 mm. Hg and the cornea clear.

I didn't get around to operating on her until about one o'clock. By that time, the cornea was not quite so clear, getting a little hazy. I didn't take her tension, but I did an iridectomy, and it went along very nicely.

Dr. Frederick Verhoeff: It is too large a subject to discuss as you all realize. I didn't have the pleasure of talking it over with Dr. Grant beforehand, so I didn't know what he was going to say. But I want to tell him that I think he has done a wonderful job. We should all be very grateful to him for this talk. It showed a lot of careful work and fine thinking. I'd like to say that about it, anyway. I don't feel qualified, without more time to think it over, to discuss it and the various details he brought out.

S. Forrest Martin,
Reporter.

MEMPHIS SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

December 14, 1948

Recurrent vitreous hemorrhages

Dr. James E. Wilson presented Mrs. S. P., aged 32 years, who was first seen on November 27, 1947. Her complaint was blurring of vision of the left eye of seven days' duration which became suddenly and mark-

edly worse the day before. She works in a dry-cleaning establishment but does not come in contact with cleaning fluid or its vapors. She has always bruised easily and, in 1940, had a hysterectomy because of profuse menstrual bleeding.

Eye examination. Vision was light perception only. The anterior segment was normal. There was a large vitreous hemorrhage below and nasally completely obscuring fundus details. The rest of the vitreous was cloudy. The disc, dimly seen, was normal. The macula appeared normal but the dim outline of a chorioretinal lesion could be seen below it. Later, when this was clearly seen, it was raised, grayish, and half the size of the disc. Subsequently the retina atrophied in this area and the edges became quite sharp. When she was first seen, there were several small bright red hemorrhages along the inferior temporal artery near the periphery. Changes resembling perivasculitis were seen along this vessel and in this area was a narrow linear old chorioretinal lesion dimly seen.

Laboratory reports. X-ray studies of the chest showed one or two old hilar nodes. The first Kahn test was doubtful but a later test was negative. Undulant and proteus agglutinations were negative, urinalysis was negative, stool examinations negative for parasites. Search for foci of infection revealed none, positive test 0.2 mg. of old tuberculin, sedimentation rate within normal limits, and blood sugar normal.

Therapy. Vitamin C, vitamin-B complex, rutin, and calcium were prescribed, and old tuberculin therapy was given in increasing dosage starting from 0.2 mg. Atropine to the eye and bed rest were prescribed.

Clearing of the hemorrhage and improvement in vision was rapid for 10 days when a moderate fresh hemorrhage came from below. At this time, because of the doubtful Wassermann and the inadequacy of the present treatment to control the condition, she was given rapid antiluetic pencillin therapy.

Gradually there was a clearing of the vitreous until only very fine stringy opacities could be seen. Tuberculin therapy was continued because of the typical appearance of the lesion below the macula. On January 3, 1948, vision had improved to 20/40. Vitamins, rutin, and calcium were continued. On March 20, 1948, vision was 20/30.

She became somewhat careless about therapy, and, on April 26, 1948, had another hemorrhage which equalled the first in obscuring fundus details. She has never before or since this complained of pain in the eye. She was give syrup of hydriodic acid and vitamin K. Special blood studies were done including complete blood count with differential and report on cell morphology, sedimentation rate, bleeding, clotting, and prothrombin time, clot retraction, platelet count, capillary fragility, and others. The only positive finding was a slight increase in bleeding time. The diagnosis as a result of these studies and her history was purpura simplex. The already large doses of vitamin C, calcium, and rutin were raised. Estrogenic treatment which she has received occasionally in the past was stopped because of its tendency to favor hemorrhage and vascular abnormalities.

The vitreous slowly cleared again until on July 23, 1948, she again had 20/30 vision. This she kept unitl August 5th, when there was another hemorrhage obscuring the fundus. This was not as dense as the former ones. The same treatment was continued and, in addition, she received from August 6th to 16th, 0.5 gm. streptomycin morning and night by injection. This was discontinued August 17th when she showed a skin rash. Satisfactory clearing of the vitreous had been taking place and vision became 20/30 and J4 on August 21st. The fundus looked essentially as described following clearing after the first hemorrhage.

She had a slight obscuration of vision on September 9th but this cleared and the vitreous was as before by the time she reported four days later.

On November 13th, she had another severe hemorrhage. Rutin, calcium, vitamin C, and tuberculin have been continued. Clearing has

been slower this time until on December 11th, vision was 20/40. Slitlamp examination for the first time shows some fine scattered posterior corneal precipitates and an occasional floating cell is seen in the anterior chamber. The fundus details remain the same. There are many stringy vitreous opacities, being densest nasally and below. On the posterior surface of the lens, over its lower one third and extending downward toward the ciliary body and slightly backward into the vitreous, is a white mass which is partly covered with bright red blood. This is interpreted as a former exudate or hemorrhage which has organized and is now covered by recent hemorrhage.

The right eye has remained normal in vision and its external and internal appearance have been normal. Bed rest did not seem to help with the first attack and has not been used since.

LESIONS OF THE CARUNCLE

DR. RALPH O. RYCHNER presented a series of Kodachrome slides representing abscess, benign nevus and cyst, chronic inflammation, and carcinoma of the caruncle with detailed reports of three of these conditions.

Cyst of the caruncle. Mrs. H. L. McK, aged 27 years, was seen September 29, 1948, with a pigmented nevus of the caruncle which was slightly enlarged with a smooth surface but with dilated vessels suggesting vascular activity. A translucent, gray, pinhead cystic mass protruded from the nasal surface. Seen in consultation with Dr. P. M. Lewis because of the possibility of malignancy, it was our consensus that the lesion should be removed and this was done under sodium pentothal anesthesia on October 7, 1948. The pathologic report by Col. R. O. Dart was:

"An epithelium-lined space near one margin may represent an inclusion cyst or simply an unfolding. Beneath this there is fat tissue divided into lobules by wide bands of collagenous connective tissue. There is no evidence of carcinoma or of any malignancy and the lesion may be on the basis of a lipoma with an epithelial inclusion cyst."

A complication of the removal was the closure of both canaliculi by scar-tissue contraction and an annoying epiphora. Neither canaliculus could be probed. Under sodium pentothal anesthesia on December 2, 1948, the lower canaliculus was dilated with the rupture of many fibrous bands. The lacrimal sac was entered with the punctum dilator. A silver style was then inserted and allowed to remain until January 5, 1949, at which time fluid was passed freely to the nose and the epiphora has ceased to date.

Chronic inflammation of caruncle. Mrs. J. J. M., aged 59 years, was seen November 23, 1948, with enlargement of the left caruncle, cystic in appearance, which overlay the lower canthal border and caused epiphora because of outer displacement of the punctum. The lesion was removed under sodium pentothal anesthesia on November 24, 1948, and the pathologic report by Dr. W. W. Tribby was:

"Enlargement of this caruncle is due to infiltration of the subepithelial tissue by lymphocytic cells which form germinal centers. The formation of germinal centers is strong evidence against lymphoid tumor. The presence of sinusoidal spaces lined by reticuloendothelial cells is also strong evidence against lymphoid tumor. There is one small focus of polymorphonuclear cells near the center of the lymphoid tissue. Near this there are several giant cells of foreign-body type. The squamous epithelium overlying this formation of cells shows rather marked and diffuse bullous edema. Enlargment of the caruncle is probably due to injury followed by chronic inflammation and foreign-body, giant-cell reaction. Microscopic diagnosis: chronic inflammation with foreign-body, giant-cell reaction, bullous edema of squamous epithelium. No evidence of tumor."

The cosmetic result was very satisfactory and the epiphora ceased.

Carcinoma of caruncle. Mr. J. D. K., aged 39 years, was observed June 29, 1946, with a mulberry enlargement of the left caruncle

measuring 6 by 15 mm. It was adherent to the skin margin at the inner canthus. A diagnosis of carcinoma was given and the enlarged caruncle removed under sodium pentothal anesthesia on July 1, 1946. Convalescence was normal but X-ray irradiation by Dr. J. C. King was begun. The pathologic report by Col. J. E. Ash was:

"Several hematoxylin and eosin sections are covered in part by atrophic, cuboidal to columnar epithelium and composed largely of fibro-fatty tissue which is infiltrated by neoplastic-type basophilic staining epithelial cells. In one section, part of the lacrimal duct is included—the lining of which has been replaced by pseudostratified columnar epithelium. This epithelium contains hyperchromatic nuclei and numerous atypical mitotic figures and shows both lymphatic and venous permeation. Some of the capillaries contain small clumps of neoplastic epithelial cells. There is moderate edema of the entire section and numerous elongated and branching basophilic-staining yeast hyphae are present. There is moderate infiltration of the subepithelial connective tissue by neutrophils and many lymphocytes. We cannot say from the material sectioned that the lesion has been completely excised. Diagnosis: Carcinoma, nasal caruncle."

On January 21, 1947, a navy-bean sized recurrence was apparent subconjunctivally behind the lower punctum. Exploration on February 4, 1947, revealed invasion of the orbit with adherence of the tumor to the internal rectus, and exenteration of the orbit was done on January 6, 1947, with the following pathologic report:

"Nests and strands of tumor cells, similar to those seen in the biopsy of July 1, 1946, invade the orbital tissues. Mitoses are numerous. There is almost no keratohyalin. Diagnosis: Anaplastic squamous cell carcinoma, primary in caruncle, invading orbit."

X-ray treatment was continued by Dr. King and, although X-ray studies of the bones never showed any infiltration and epithelization of the socket continued at a normal rate, there was some enlargement of the sublingual glands apparent by February 20, 1948. The patient was subsequently seen at Barnard Hospital, St. Louis, with metastasis to the left anterior cervical lymph nodes and surgical excision of the lymph chain was advised. Consultation at the Mayo Clinic this past summer resulted in the implantation of radon seeds into the enlarged lymph nodes with some regression in their size. The patient still looks surprisingly well.

Retrolental fibroplasia

Dr. Ralph O. Rychener reported two cases of retrolental fibroplasia.

Case 1. A. Y., aged 10 months, a girl, was seen on September 12, 1947, because of the diagnosis of congenital cataract by her home physician. The anterior chambers were shallow, although the irides reacted to light. A gray membranous mass behind the lens obscured the fundus details except in the right eye where the optic disc and a small region of retina surrounding it were visible. The disc was pale and extensive pigmentary degenerative changes were observed in the retina.

The left chamber was shallow, posterior synechias and iris atrophy were present, and a similar retrolental membrane with marked pigmentary changes in the retina was observed. The eyes were small and enophthalmic. Intraocular pressure was increased, registering 58 mm. Hg and 45 mm. Hg (Schiøtz) and miotics were prescribed.

No appreciable changes have taken place in a course of the past four months but the intraocular pressure has been maintained at levels of 23 mm. Hg to 31 mm. Hg (Schiøtz) by the installation of neosynephrin solution (2.5 percent) four times daily.

Case 2. R. J., aged seven months, a girl, was seen on December 2, 1947, with a history of premature birth at six months' gestation, incubation, and hospitalization until term, since which time general health had been normal.

It was observed after the age of one month that there was a cloudiness of pupils. The anterior chambers were empty, the irides were blue and poorly developed, with pupillary membranous remnants attached to the lenses. The lenses were clear but the anterior portion of the vitreous was filled with a grayish-white membrane with vessels present on the surface in the right eye. Intraocular pressure was 25 mm. Hg (Schiøtz).

In view of the consistently poor results reported by surgical measures, the advice given by a colleague for surgical removal of the lenses and the membranes was not confirmed. A few days later this patient was seen by another colleague from a large eastern clinic at his home city in Mississippi. Surgery was advised and the patient died from the effect of the anesthesia before conclusion of the operation.

Considerable literature has been accumulated since Terry's intensive study of this subject but, although many forms of treatment have been advocated, none to date has yielded any satisfactory results. Krause examined 18 cases of encephalo-ophthalmia dysplasia of unknown origin. Retrolental masses and other histologic aberrations of the eyes, particularly in the retina, were present. Both surgical and medical measures were found to have no effect to prevent or cure the disease. Private communications with Dr. Beetham, Dr. Reese, and Dr. Guyton showed that no treatment had so far been successful in the control of this disease in Boston, New York, and Baltimore. Various surgical measures, such as removal of the lenses and resection of the retrolental membranes, have resulted only in deterioration of the globes.

Secondary glaucoma after cataract extraction

Dr. Philip Meriwether Lewis reported a case with several interesting complications following cataract operation.

Mrs. W. B., white, aged 58 years, had posterior subcapsular cataracts of both eyes. A combined intracapsular extraction was done on the right eye in January, 1947. Mild iritis and an allergic reaction to atropine were the only complications. Corrected vision was 20/20 and J1.

On November 6, 1947, a combined intracapsular extraction was done on the left eye. This was followed by failure of the anterior chamber to reform. No leak of the wound could be demonstrated with fluorescein. The patient insisted on going home and did not report for observation for two weeks.

At that time the chamber had restored slightly above, but the lower two thirds of the iris was plastered against the back of the cornea. The vitreous protruded through the pupillary space and in its lower half rested in contact with the cornea. The cornea was clear and the tension was 30 mm. Hg (Schiøtz). She had no pain and thought that her eye was doing fine. Strong miotics were used alternately with neosynephrin (10 percent) without change in appearance.

She did not return for three weeks at which time she had severe pain. The cornea was steamy and the tension 60 mm. Hg. Cyclodialyses in the lower nasal quadrant and in the upper temporal quadrant were performed with injections of air. Following these procedures the pressure remained normal for one month. She then developed an attack of acute glaucoma which prostigmin made worse. An anterior sclerotomy with injection of air lowered the pressure to normal for about 10 days.

During the prolonged course of treatment, the patient developed successively an allergic reaction to atropine, pontocaine, scopolamine, eserine, and metaphen.

On January 24, 1948, the tension had risen again to 60 mm. Hg (Schiøtz). Preparations were made for another cyclodialysis, but the retrobular injection caused a severe intraorbital hemorrhage with extreme proptosis. The pressure remained high for about two weeks and then gradually fell to the low twenties where it has remained since.

In spite of the complications, good useful vision, 20/25—J3, was finally obtained.

KERATITIS TREATED WITH SILVER NITRATE

DR. S. B. CARUTHERS presented the case of Mrs. J. B. H., a white woman, aged 23 years, who was first seen on December 29, 1947, complaining that her left eye had been hurting for two months. An oculist had fitted her with glasses without benefit. On examination, she was found to have superficial punctate keratitis with many fine pinpoint vesicles of the cornea which stained with fluorescein. She was given 10-percent dionin, three times a day for three days, then ophthalmol A and D, three times daily, regularly.

On January 5, 1948, the patient was feeling much better and only one small pinpoint ulcer showed on the cornea. She was given smallpox vaccine, since it was thought that this might be a virus infection, and was told to continue dionin for three days and ophthalmol for four days and to return in one week.

Four days later, however, she returned because the eye condition had flared up. New ulcers were present. She was given pontocaine ointment for the pain and previous medication was continued until February 2nd. Since she was no better, under cocaine anesthesia, tincture of iodine was touched lightly to three small vesicles on the left cornea. Three days later she was feeling better, but two areas still stained with fluorescein.

One week later, there was a severe flare-up. The patient was given 5 cc. of protelac, and an appointment was made with Dr. J. B. Stanford of Memphis. On February 13th, Dr. Stanford reported: "We agree that the diagnosis is superficial punctate keratitis. The lesions are practically all in the palpebral fissure, so it might be well to keep a dressing on the eye. Also, we suggest that you apply a drop of the patient's blood to the cornea daily before dressing. We suggest also that you do a basal metabolism rate and give thyroid if indicated. If these measures do not cure the condition, try methylene blue and a 10-second exposure to ultraviolet light."

On this day, February 13th, a drop of the patient's blood was applied to the cornea, and she was told to apply one drop daily at home. The basal metabolism rate on February 17th, was a minus 20. The eye looked better with no definite staining, and she was started on 0.5 gr. thyroid extract, three times daily. On February 24th, 1 or 2 little spots in the eye stained with fluorescein, and one drop of blood was applied to the eye. She was told to increase the thyroid tablets to 2.0 gr. a day. The eye was dressed at each visit.

On March 2, 1948, tht eye did not hurt, but there were numerous, pinpoint, staining areas. The pulse rate was 76. She was ordered to take two 0.5-gr. thyroid tablets three times daily, to go back to dionin for three days, and to leave the dressing off for a week. On March 8th, both eyes began to pain and the condition looked a little like an allergic reaction. An orris-root test was plus-three positive. She was advised not to use cosmetics, to apply pontocaine ointment for pain, to use estivin eye drops, and to take 50 mg. benadryl four times a day. Three days later, the condition was improved, but treatment was continued.

By March 18th, however, both eyes were worse, inflamed, and showing more pinpoint ulcers. A telephone call to Dr. Stanford's office was answered by Dr. Wilson who suggested that one drop of 0.5- or 1-percent methylene blue be applied to the eyes, followed in a few minutes by 5- to 10-seconds' exposure to ultraviolet light, this treatment to be repeated every 4 or 5 days. One cc. promanulake should be given intravenously, one eye should be kept bandaged all the time, both as much as possible, and another drop of the patient's blood applied in each eye.

One month later, vision was: R.E., 20/25+2; L.E., 20/20−1. Numerous punctate staining areas were still present. Two-percent silver nitrate was applied to the conjunctivas of both eyelids.

On April 20th, the eye looked better but a few spots on the corneas still stained. Silver nitrate (2 percent) was again applied to the

conjunctiva of both of the eyelids.

In the meantime, I received a package library on superficial punctate keratitis from the American Medical Association. There were many articles reporting hundreds of cases, most of which, I found, referred to the epidemic type of keratoconjunctivitis. However, one paper by a New Zealand doctor reported about 100 cases similar to mine. One half of these had been treated by the application of 2-percent silver nitrate to the eyelids; the other half, control, had not been so treated. All of the cases treated with silver nitrate had cleared after an average of 1.5 to 2 treatments; a few required 5 or 6 treatments.

The same silver-nitrate treatment was used on my patient on April 20th and 27th, May 13th, 20th, and 27th, and on June 10th. Since that time, she has had no more trouble.

Dislocation of lens into anterior chamber

Dr. Philip Meriwether Lewis presented Mr. E. L. A., white, aged 34 years, who was seen on September 10, 1948, because of severe pain in his right eye, which began the previous night. The pain was due to the lens being in the anterior chamber, and the intraocular pressure was 55 mm. Hg. (Schiøtz). The patient had diagnosed the condition himself, because four years previously the same thing had happened to his other eye and the lens had been removed at the Memphis Eye, Ear, Nose and Throat Hospital. In March, 1945, he was presented before this society, with corrected vision of 20/20−J1 in his aphakic eye. Previously he had never had better vision than 20/100 in either eye due to congenital dislocations of both lenses.

On the afternoon of September 10, 1948, the lens was removed through an incision made below. There was no loss of vitreous and no difficulty in replacing the iris, so that a perfectly round pupil resulted. This man was rather tall and thin, but showed no other signs of arachnodactyly. There was no history of any ocular defect in other members of his family.

Fracture of orbit and facial bones

Dr. D. H. Anthony and Dr. Daniel F. Fisher reported the case of Mr. C. L. W., a white man, aged 36 years, who was in an automobile accident on the afternoon of August 13, 1948. He was seen five hours later. His general condition was good but he had acute discomfort in his face. Temperature was normal. There was contusion and swelling above the right frontal region, the eyelids were swollen closed but could be opened by forcing. There was a moderate degree of enophthalmos and the right eye was considerably lower than the left. Vertical diplopia was present in all directions. There was considerable swelling over the right malar region with tenderness over the entire right side of the face and over the zygomatic region.

X-ray films made that night at our office showed fracture of the outer rim of the right orbit (through the zygomatico-frontal suture) and displacement of the lateral wall nasally, fracture through the lower rim of the orbit, mid portion, and marked depression in the lateral fragment downward into the antrum, and fracture of the zygomatic arch without much displacement. There was a fracture of the upper jaw so that it could be rocked, but there was no displacement. The patient was edentulous. Because of the patient's discomfort, only an estimation of visual acuity was made, which was apparently normal. Ophthalmoscopic examination was normal. The patient was hospitalized at the Memphis Eye, Ear, Nose, and Throat Hospital and operated the following morning.

Operation was performed locally under H.M.C. and nembutal; novocain and cocaine were used locally. Incision was made through the right canine fossa and the loose fragments of crushed bone from the anterior wall of the antrum were removed and the sharp edges of bone smoothed. It could then be seen that the fracture through the floor

of the orbit was considerably more extensive than the X-ray films had indicated and extended for the entire length, with the lateral portion displaced downward for the entire length of the antrum. A huge amount of orbital fat had prolapsed into the antrum.

The fractured bones were mobilized and pushed back into place. A medium-sized intranasal antrostomy opening through the inferior meatus was made.

A Shea water balloon was inserted through this opening into the sinus, and 35 cc. of water were forced into the balloon. A wait of at least one minute was made between giving of each five cc. A metal clamp was placed on the stem of the balloon and the canine fossa closed by chromic catgut. Pain was controlled by pantopon and nembutal.

Two points should be mentioned: (1) The antrostomy opening should not be too large, otherwise a portion of the balloon may protrude into the nasal cavity; (2) the fluid must be introduced into the balloon carefully, allowing a few minutes between each dose for the balloon to push up the fractures, otherwise there is danger of blowing the stem of the balloon off from the sac portion. This has happened to us on two previous occasions.

X-ray films made in our office four days later showed the fractures reduced and in proper position, and those made 13 days following operation gave an excellent view of the balloon in place. The opaque material injected into the balloon is 25-percent barium, with 5-percent acacia added to hold the barium in emulsion and with 3-percent phemerol added to prevent the solution souring.

At the time the barium pictures were made, the patient's vision was normal in both eyes with a small hyperopic astigmatism correction; ophthalmoscopic examination normal; and muscle balance showed exophoria of three diopters, and right hyperphoria of three diopters. The balloon was removed at this time, 14 days after the accident. It is interesting to note that, even with the extensive displaced fracture of the floor of the orbit and the tremendous prolapse of orbital fat, only a moderate degree of enophthalmos and drooping of the right eye was produced. However, we are certain that the extensive edema accounted for this.

Cosmetic results and eye-function results in this case were considered to be excellent. The antrostomy opening has, of course, been enlarged somewhat by pressure of the balloon with the result that this damaged antrum has a good permanent opening. This is quite essential in cases in which damage to the membrane of the sinus is as extensive as in this case for such damage predisposes to recurrent sinus infections.

Goniotomy for congenital glaucoma

Dr. J. Wesley McKinney reported the case of G. W. C., an infant, who was first seen on April 13, 1948, at the age of eight months. The eyes had appeared hazy and slightly enlarged since the age of three months. There had been photophobia and some lacrimation.

Examination revealed faint pericorneal injection. The corneas were enlarged and edematous with diffuse and somewhat streaked stromal opacity. The anterior chambers were deep and the pupils reacted normally. Only a faint fundus reflex was seen.

On April 15, 1948, under ether anesthesia, both corneas measured 13 mm. in horizontal diameter. With the contact glass, the angles could be seen but no details could be made out due to the corneal clouding. Tension was: O.D. 30 mm. Hg. (Schiøtz); O.S., 37 mm. Hg. At this time goniotomy was done on the right eye. Edematous corneal epithelium was scraped off the right cornea in preparation for the goniotomy. This cleared the cornea sufficiently so that the angle was seen well enough to operate under the surgical contact glass although the fine details of the angle structure could not be made out. The angle was freed with the goniotomy knife from the 6-o'clock to about the 3-o'clock positions. A little blood

appeared over the iris after withdrawal of the knife.

On April 20, 1948, under ether anesthesia, gonioscopy was done on the right eye. The angle seemed to be free in the area of previous goniotomy but the details could not be well seen due to the haze of the corneal stroma. The tension was 23 mm. Hg (Schiøtz). At the same time a cyclodialysis was done on the left eye from the 10-o'clock to the 2-o'clock positions.

On April 29, 1948, under ether, gonioscopy on the left eye revealed the angle to be free above in the operated area but no cyclodialysis cleft could be seen. The tension was: O.D., 25 mm. Hg; O.S., 23 mm. Hg.

On May 22, 1948, the tension had again risen and, under ether anesthesia, was found to be: O.D., 30 mm. Hg; O.S., 52 mm. Hg. In preparing for goniotomy on the left eye, the needle for the fixation suture penetrated the sclera with loss of aqueous and collapse of the anterior chamber necessitating postponement of the operation.

On June 26, 1948, goniotomy was done on the right eye in an unoperated area from the 3-o'clock to 1:30-o'clock positions and on the left eye from the 10-o'clock to 7:30-o'clock positions. There was little reaction from the procedure. The eyes remained white and clear; photophobia and lacrimation disappeared and the tension seemed normal.

On August 28, 1948, two months after the last goniotomies the child was put under ether for a final check-up. There remained a faint diffuse opacity of the corneal stroma of each eye. The angles were free in the areas of goniotomy and the tension was O.D., 23 mm. Hg; O.S., 21 mm. Hg. In a recent communication, the mother stated that the eyes were clear and that there was no photophobia or lacrimation. The child seemed to see well.

Stone-Jardon implant

Dr. Ralph O. Rychener presented Miss L. J. R., whose left eye had been enucleated 2½ weeks previously because of traumatic laceration of the sclera. The Stone-Jardon implant with plastic conformer had been inserted with excellent results to date. Although the conjunctiva and capsule had retracted to expose a limbal area of the tantalum mesh, there was no reaction in the orbit and the movement of the plastic conformer was excellent.

Vitreous prolapse into anterior chamber

Dr. D. F. Fisher presented a Negro, W. W., aged 60 years, who was examined in September 1948, stating that he had been struck in the left eye by a piece of wood and that his vision had failed since that time. His right eye had been injured in childhood and had been shrivelled and blind since that time.

Examination showed: R.E., quiet phthisis bulbi; L.E., fingers at one foot. There was no evidence of any injury and, as far as we could determine, there was a mature senile cataract, uncomplicated. His blood pressure was 200/115 mm. Hg. X-ray pictures were taken of his eye as a precautionary measure, but no foreign body was evident. X-ray studies of the teeth showed no foci of infection.

On October 21, 1948, an intracapsular lens extraction with peripheral iridectomy was performed. Sutures were of the Castroviejo type. The eye had a very normal course for about five days, at which time the anterior chamber became nearly flat. No evidence of choroidal detachment was present.

On his first visit to the office, 14 days after operation, slitlamp examination showed an intact hyaloid, but with the vitreous mushroomed into the anterior chamber and pushing the iris forward. The patient's vision was 20/25 with a +11D. sph. and J1 with +14D. sph. Atropine was continued for three weeks and, as soon as the pupil came down, most of the vitreous receded and the chamber deepened to approximately normal.

Daniel F. Fisher,
Recorder for Eye Section.

AMERICAN JOURNAL OF OPHTHALMOLOGY

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ON LECTURESHIPS IN OPHTHALMOLOGY

The number of lectureships has risen so rapidly in the United States that a consideration of their purpose may be justified. A brief list of the lectures which are given annually with one exception is the following:

A Jackson Memorial Lecture has been given since 1944 at the meeting of the Academy of Ophthalmology and Otolaryngology and is sponsored by the Ophthalmic Publishing Company. A second memorial Jackson Lecture has been presented before the Colorado Ophthalmological Society since 1944, and is under the joint auspices of the Colorado Ophthalmological Society and the University of Colorado.

A yearly lecture is given at a meeting of the Section of Ophthalmology, New York Academy of Medicine, by a request of Mrs. Rosalie A. May in 1947 in memory of her husband. The lecture is known as the Charles H. May Memorial Lecture.

The Mark J. Schoenberg Memorial Lecture was sponsored in 1946 jointly by the National Society for Prevention of Blindness and the New York Society for Clinical Ophthalmology. The lecture is given at a

regular meeting of the New York Society of Clinical Ophthalmology. The subject of the lecture is preferably something in which Dr. Schoenberg was interested.

The Chicago Ophthalmological Society founded a Gifford Lectureship in 1944, in memory of Dr. Sanford R. Gifford. This lecture is given at a meeting of the Chicago Ophthalmological Society.

The Section on Ophthalmology of the College of Physicians of Philadelphia established a de Schweinitz Lecture, in 1937, which is given at one of its meetings.

The Francis I. Proctor Lecture on Ophthalmology was established in the University of California in 1946 by Mrs. Proctor, in memory of her husband, and is given at the end of the lecture course which the Division of Ophthalmology of the University of California Medical School holds every fall.

In Boston there is a Howe Lectureship in Ophthamology sponsored by the Howe Foundation which is given only from time to time because of some particular circumstance.

The Estelle Doheny Lecture is presented by the Estelle Doheny Eye Foundation in Los Angeles. The lecture, an integral part of the Foundation's function, is named for Mrs. Edward Laurence Doheny the Foundation's benefactress, who, in establishing the Foundation on August 1, 1947, dedicated it irrevocably to further "the conservation, improvement, and restoration of human eyesight." The lecture is given in Los Angeles, under the auspices of the Los Angeles Society of Ophthalmology and Otolaryngology.

Dr. Joseph Schneider, of Milwaukee, left a sum of money to the Interstate Postgraduate Medical Association of North America, the income of which was to be used in promoting the investigation of constitutional diseases and their relationship to the eye. This led to the establishment of a lecture which is delivered every year at the annual meeting. The bequest is called the Schneider Eye Research Foundation and it is probably one of the earliest in this country devoted to this special field.

These 10 lectures make a serious demand on suitable speakers and on appropriate topics. When the supply of speakers is inadequate and sufficiently new subjects are not available, the purpose of the lectureship suffers and the project loses in dignity and prestige. The simplest remedy under existing conditions consists in giving the lectures not as a yearly event but only when the circumstances warrant.

The desire to honor the name of an outstanding ophthalmologist who has made a real contribution to ophthalmology during his life is most praiseworthy and should be encouraged but, in the future in place of more lectures, may I suggest a substitute in the form of a prize.

This prize consisting preferably in a money stipend and not a medal should be bestowed for the report of original laboratory or clinical investigation which has been accepted by a committee of one of our national societies. This investigation is to be published under the name of the author as recipient of the prize in question. This would serve as a stimulus for the young laboratory or clinical worker.

Arnold Knapp.

THE PRESENTATION OF PROJECTION SLIDES

There can be no doubt of the value of good illustrations in the presentation of a paper at a medical meeting. The recent Academy meeting emphasized some points that would seem to warrant a few comments on this subject.

Most medical centers have good photographic departments that make creditable projection slides. In addition, the great advances in amateur photography have made it possible for the interested individual to produce his own slides, so that there should be no excuse for poor slides.

With the advent of adequate projection, there has been a tendency to use 2 by 2 slides. They have many advantages: they are inexpensive, take up little space, and mate-

rially reduce the weight, an important factor for the traveler. In addition they make color readily available and there can be no doubt of the value of color in projection slides.

If the 2 by 2-size slides are used, they must be photographically good, for poor slides of this type, when projected, tend to exaggerate the defects that may be present. There are certain fundamental principles that must be considered if the projection of illustrations is to be effective. Anything that tends to detract from the data the slide is attempting to point out must be avoided.

If color slides are used they should be properly exposed; also, they must be in focus, as colored illustrations out of focus are very uncomfortable to the observer. They should be mounted in glass so that they can be easily focused and the focus maintained during projection. The cardboard mounts furnished by the processors of color are unsatisfactory as the film has a tendency to buckle when it becomes heated. Glass slides also protect the films against damage. It is well to remember that one poor picture may detract so much that the good ones are forgotten.

Care should be taken that the illustrations are projected right side out and not "up side down." If the photograph of a drawing is projected with the artist's name "up side down" and backward the audience has a tendency to attempt to decipher the name rather than to observe the data presented.

Slides should be clean: finger prints, particles of dust, and smears detract a great deal.

In the use of slides, it is important that data projected be confined to the area of the slide normally used; the masks for both types of slides are standardized as to the space used for projection. If this is not observed the author may find that the most important part of the slide is off the screen. This happened a number of times at the recent meeting. The above precaution is especially important if 2 by 2 slides are used.

When typing is used, a common mistake is to include so many lines that it is not legible. In the preparation of typing for slides, a new ribbon should be employed and not over 12 lines double spaced used. Another fault is attempting to get so much material on a single chart that when it is projected it is not readable.

When high-power microphotographs are used, they should always be preceded by a low-power projection so that the audience can orient itself.

Slides to be used at a medical meeting should be prepared well in advance so as to allow sufficient time to replace any defective illustrations.

When the slides are given to the projectionist, they should be in proper order and be properly marked in the upper right hand corner by a small paper disc or star. In the preparation of Kodachrome slides, the dull surface should be toward the screen and the slide should be upside down. When the slides are projected, the author should speak from the slide or glance at the slide to be certain that it is in focus since there is a tendency among projectionists to set the instrument at one point and not bother to readjust the focus for various slides. It is usually essential that the author point out the important features of the illustration.

If illustrations are to be used during the presentation of a paper, they must pertain to the subject, must be clean, in good focus, and readily readable if the audience is to be held, otherwise, with the lights off, a warm room, and poor slides, there is a tendency to take "40 winks" while the author drones on.

Frederick C. Cordes.

CORRESPONDENCE

Effect of retrobulbar anesthesia on ocular tension and vitreous pressure

Editor,
American Journal of Ophthalmology:

In your October issue I read a paper by Dr. Harold Gifford, Jr., entitled "A study of the effect of retrobulbar anesthesia on ocular tension and vitreous pressure."

I wish to make a few comments on the paper. Some years ago I made a study of

"Retrobulbar anesthesia effects and ophthalmotonus," issued in the Brazilian review, *O Hospital*, October, 1945.

In the material dealt with, the tension was taken before any anesthetic was used, except one drop of 0.5-percent tetracaine, and then, in the first group, after five-percent cocaine-adrenalin repeated instillations; in the second group, after cocaine (five-percent) instillation; in the third group, after retrobulbar anesthesia with four-percent novocain-adrenalin; and in the fourth group, with retrobulbar injection of novocain (four-percent) without adrenalin. I saw a tension-lowering effect in each group that was greater when adrenalin was added. I concluded also that the lowering effect of cocaine-adrenalin instillation was greater than that of retrobular injection of four-percent novocain-adrenalin. The lowering appeared in 4 to 5 minutes after the injection.

(Signed) Evaldo Campos,
Rio de Janeiro, Brazil.

Toxicity of T.E.P.P.

Editor,
American Journal of Ophthalmology:

Since preparing a report* on the ocular evidence of toxicity from tetraethyl pyrophosphate (Parathion as used for crop dusting), I have been informed of several deaths from this substance.

In discussing this report, Dr. Wilson T. Sowder, state health officer, said that spraying with T.E.P.P. had been so effective against insect pests, and had so improved the crops, that it would not be discontinued, but the crop dusters must take proper precautions and doctors must be familiar with toxic symptoms and be prepared to treat any case of T.E.P.P. poisoning as an emergency.

T.E.P.P. has the same pharmacologic actions as D.F.P., and the eye signs of T.E.P.P. poisoning are recognizable early. The antidote is atropine (1/100 gr.) repeated until dilatation of the pupils occurs. In addition to the miosis and ciliary spasm (lens fixed for near vision), the intraocular pressure will be found to be lowered.

It is reported that there may be striated muscle fasciculations, increased gastro-intestinal tone with abdominal cramps, diarrhea, nausea, vomiting, perspiration, lacrimation, salivation, restlessness, bradycardia, cardiospasm, complete auricle ventricular dissociation, constriction of bronchial muscles, increased secretion of bronchial glands, convulsive seizures that may be epileptiform.

Death may occur from bronchial spasm, overstimulation of autonomic effector cells, from central stimulation followed by depression, or from stimulation followed by depression of striate muscles which, if death does not occur, may be followed by muscle paralysis as in Jamaica-ginger poisoning of the prohibition era. If the patient survives 24 hours he will live, hence the urgency for immediate treatment.

(Signed) Garland M. Johnson,
Fort Lauderdale, Florida.

* Read before the Southwestern Medical District, Sebring, Florida, October 27, 1949.

BOOK REVIEWS

VOLUME IV*

Cui mens divinior, atque os
Magna sonaturum, des nominis huius honorem.
Horace, Sat.
(He alone can claim this name, who writes with fancy high and bold and daring flights.)

"I must apologize for the delay in the appearance of this volume, but six years of military service far from the study and the library have not been conducive to the compilation of a book of this type." (Note picture above.)

"But it was in 1932 that the author rendered his greatest contribution to ophthalmic science. In this year the first edition of Volume I of his *Textbook of Ophthalmology* appeared. This first volume alone, of more than a thousand pages dealing with the De-

* Textbook of Ophthalmology. By Sir Stewart Duke-Elder, K.C.V.O., M.A., D.Sc. (St. And.), Ph.D. (Lond.), M.D., Ch.B., F.R.C.S., F.A.C.S. (Hon.), D.Sc. (Hon. Northwestern). St. Louis, the C. V. Mosby Company, 1949. Price, $20.00.

Volume IV in preparation, during a holiday in Kent and a well-earned and rare week-end leave from hazardous military service, just before D-day.

velopment, Form, and Function of the Visual Apparatus, would have been enough to bring the author fame and to make him worthy of the honor we wish to bestow upon him today. It contains approximately 600,000 words, but not a single superfluous one. To put my personal opinion in a nutshell:—It is the most complete, comprehensive, comprehensible, and compressive compilation of the subject in existence. A continental critic wrote shortly before the war that it was astonishing how one single man could be the author of this volume as it would need about a dozen continental scientists to compose a textbook of equal standing.

"Since then Volumes II and III have left the press and the startled world of ophthalmologists learned that the author is as good an authority on the pathology of the outer and inner eye as he proved himself to be on anatomy and physiology. After the standard previously mentioned, the author equals now about three dozen of continental scientists! There are rumors that he is preparing a fourth volume and how welcome it will be to all of us! But I fear that I will lose count of the equivalents. At any rate (I fear) that the continent will not be able to supply the necessary number of scientists." Professor H. J. M. Weve, speech on presenting the Donders Medal, 1948.

Well, here is Volume IV, beautifully conceived, skillfully written, and admirably illustrated. It covers the subjects of the Neurology of Vision, the Motor and the Optical Anomalies of the Eyes. It contains 1,081 illustrations including 71 in color, 1,154 pages, and goodness knows how many words of flowing beauty and precise meaning. If it has taken six war years to write, it will take more than that of years of peace to read, study, digest, and make the information it contains an integral part of your intelligence.

—Nil fuit unquam
Sic dispar sibi—
Horace.
(Sure such a various creature ne'er was known)

Every scientist and physician echoes and endorses these eloquent words of Professor Weve:

"But what we admire in your books is not only the vastness of your knowledge, not only the extent of your reading, your astonishing erudition, but your gift to select from the enormous world literature exactly what is really of importance. We admire perhaps even more the spirit of fairness that urged you to give every honest opinion an honest chance."

Cum talis sis, utinam noster esses!
Horace.
(Could we but call so great a genius ours.)

Derrick Vail.

LE PARSLISI DEI MUSCOLI OCULO-MOTORI ESTRINSECI. SINTOMATOLOGIA E DIAGNOSTICA. By Marcello Focosi. Rome, Via Levico 11, Abbruzzini Editore, 1948. 585 pages, illustrated. Price, 2,800 lire.

In the first part of this book (pages 3 to 60), Focosi surveys in detail the anatomy of the nervous pathways governing the movements of the eyes and gives a brief anatomic

description of the extraocular muscles. In the second part (pages 63 to 78), the physiology of binocular vision and of the eye movements is summarized. The third part (pages 81 to 147) deals with the general symptomatology and the diagnostic procedures as well as with the special symptomatology of the paralyses of the extraocular muscles. The author's approach in these chapters is sound and his exposition lucid.

Next (part IV, pages 145 to 243) the supranuclear and infranuclear paralyses are discussed exhaustively, particularly insofar as they are of help in the topical diagnosis of intracranial lesions.

The last and largest section of the book (part V, pages 247 to 549) is devoted to the etiology of the paralyses of the extraocular muscles. It treats in great detail of the congenital anomalies of the ocular motility and of the disorders of the extraocular muscles found in acute and chronic infectious diseases, in intoxications, in diseases of the metabolism and other systemic disorders, in infectious and organic nervous lesions, and so forth. This section with its rich bibliography is particularly valuable. It is the most comprehensive and at the same time the most compact treatment of the subject which has come to the attention of this reviewer.

There are a number of typographical errors, particularly in the spellings of non-Italian names and in the bibliography, but on the whole the book is well got up. It should be of real service to any ophthalmologist who is able to read Italian.

Hermann M. Burian.

AUGENSPIEGELKURS (Course in Ophthalmoscopy). By Dozent Dr. Peter Siegert, Chief of the Eye Department of The General Hospital St. Georg, Hamburg. Hamburg, H. H. Nölke, Verlag, Ed. 3, 1947. 131 pages, 50 illustrations, index. Price, not stated.

The author in his introduction remarks that this concise volume is intended as a stopgap for medical students until standard textbooks of ophthalmology again become available in Germany.

A brief first chapter deals with the theory and use of the ophthalmoscope. It is surprising to note that the electric ophthalmoscope still is not considered in Germany an instrument suited and essential for the general practitioner, and receives only brief mention. Even a Recoss disc seems out of the reach of the medical student or general practitioner, so he will have to depend mostly on the indirect method, although the direct method is described and its limitations are explained if no correcting lenses are available.

The various physiologic and morbid pictures met during the study of the eyeground are described in painstaking detail. In every instance, the morphologic appearance is reduced to its anatomic principle and the mechanical and physical factors that produce the significant changes are given. Again and again the peculiarity of a tissue-specific response to dissimilar insults is emphasized; that is, it is quite impossible to draw diagnostic conclusions from the ophthalmoscopic picture as to the specific nature of an inflammatory lesion.

Controversial views are avoided, and the material presented may seem oversimplified. For didactic reasons, such an approach is welcome; the student introduced to a new field otherwise might easily become bewildered. Thus, it may be overlooked that, for instance, the presentation of glaucoma seems somewhat dated in view of more recent concepts of the factors leading to the fundus changes characteristic of this entity.

Particularly enjoyable reading is the discussion of optic atrophy, especially the inclusion of certain pupillary abnormalities. It is obvious that the author has grown up in the atmosphere of Behr. In a concluding section, visual field changes and their correlation to the apparent fundus changes are described. It is stressed that frequently a definite diagnosis of an ophthalmoscopic picture depends on the significance of the visual field.

The tremendous material covered in this

treatise could be presented in such brief form only by strict avoidance of repetition, and by the inclusion only of the essential. Every phrase is carefully worded, and this little volume could well become a classic for this particular topic.

The author is well aware of the paucity of the illustrations; but it was the best that could be done under the circumstances.

An English translation of the book is highly desirable.

Stefan Van Wien.

HET RUBELLA PROBLEEM IN HET LICHT VAN NEDERLANDSCHE ERVARINGEN (Dutch Experiences About the Rubella Problem). By Dr. A. Elisabeth H. M. Kamerbeek. Leiden, Stanfert Kroese, 1949.

The author starts with an extensive review of world literature. In the Netherlands she was able to collect a series of 105 cases of congenital defects in children whose mothers had been suffering from rubella and of seven children with congenital defects of whom it was sure that their mothers had been in contact with rubella during one of the first months of pregnancy.

Investigating the nature and the extension of the defect in relation to the moment at which the mother was infected or exposed to infection, Dr. Kamerbeek found that the earlier the infection took place, the more serious the defect in the child became, thus confirming Carruther's theory.

In drawing a diagram representing the number of rubella cases and the number of children having congenital defects, Dr. Kamerbeek found in her Dutch material two parallel toplines.

In comparing mothers of children with congenital deaf-mutism with mothers of normal children, it was found that, in the first group, the frequency of rubella in the mothers was much higher. The chance of a congenital defect in the child seems to be very great in the first two months of pregnancy. For prophylaxis, the passive immunization was chosen.

The author stresses the point that rubella is definitely an important illness, not merely a nuisance, and points to the significance of the white differential cell count.

Finally, she discusses the necessity of studying the epidemiology of rubella which can only be done in coöperation with the family doctor and by adding rubella to the list of reportable diseases in the Netherlands.

J. Alexander Van Heuven.

BLAKISTON'S NEW GOULD MEDICAL DICTIONARY. Edited by H. W. Jones, M.D., Col. U.S.A. (Retired); N. L. Hoerr, M.D., Ph.D.; and A. Osol, Ph.D., with the assistance of an editorial board and over 100 contributors. Philadelphia, The Blakiston Company, 1949. 1294 pages; 252 illustrations, 129 in color. Price: Textbook edition, $8.50; thin-paper edition, $10.75; deluxe edition, $13.50.

"There is for every thought a certain nice adaption of words which none other could equal, and which when a man has been so fortunate as to hit, he has attained, in that particular case, the perfection of language." (Boswell, *Life of Samuel Johnson.*)

According to the publishers, this is the first new medical dictionary in 38 years. It is obvious that painstaking care has been taken to make it complete. The contributor for ophthalmology is Lorand V. Johnson, M.D., associate professor in ophthalmology, School of Medicine, Western Reserve University, who has done a good job. There are many attractive features; for example, short biographical notes on the scientists who have contributed to medicine something that bears their names, useful charts and tables, as well as illustrations, a system of modern phonetic respelling, alternate pronunciations, and cross references. All branches of medicine are covered. It is a beautiful and useful tool and strictly up to date, so throw away the dictionary you have been using since your medical school days.

Derrick Vail.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

2

GENERAL PATHOLOGY, BACTERIOLOGY, IMMUNOLOGY

Cutinelli, C., and Bonavolonta, A. **Lysozyme in suppurative disease of the eye.** Giorn. ital. oftal. **2**:19-25, Jan.-Feb., 1949.

The authors found no lysozyme in the aqueous and vitreous of eyes with nonsuppurative diseases. It appears in noticeable quantity in these humours when a suppurative condition exists such as hypopyon keratitis and septic endophthalmitis. This shows the importance of the leucocytes in determining the amount of lysoyme in the tissues and, aside from their antibacterial action, in bacteriolysis. Vito La Rocca.

Gill, W. D. **Ocular allergy: allergic phenomena affecting the eye and its adnexa.** Arch. Ophth. **42**:238-248, Sept., 1949.

Dermatitis of the eyelids and conjunctival edema, vernal conjunctivitis, conjunctival folliculosis, subconjunctival hemorrhage, retinal hemorrhage and optic neuritis may be due to allergy and this paper lists many more. It is interesting to note that eosinophilia in the conjunctival secretions does not occur in physostigmine or pilocarpine conjunctivitis but does occur in atropine and homatropine conjunctivitis. The significance of this difference is controversial. Atropine may produce an allergic reaction in the eyes but the absence of eosinophils in pilocarpine and physostigmine conjunctivitis suggests that the latter is toxic rather than allergic.

In follicular or in vernal conjunctivitis, the discharge from the eye is heavy with eosinophils. The occurrence of a few pink-stained leukocytes in the smear is not enough; to be diagnostic, the cells must contain visible eosinophilic granules. An increase in basophilic leukocytes has also been noted in allergic conjunctivitis and vernal catarrh by Thygeson, who observed that they sometimes outnumbered eosinophils. Generally speaking, polymorphonuclear neutrophils are characteristic of bacterial infections, mononuclear cells of virus infections, eosinophils and basophils of allergy. Tuberculosis in the eye may be considered an allergic disease. In syphilis the reactions in the eye are considered allergic manifestations due to some protein-like substance elaborated in the

course of the disease. While sympathetic uveitis may not be entirely an allergic disease, there is an allergic phase in which a definite sensitization to uveal pigment exists. Verhoeff and Lemoine described a type of allergic reaction in the eye, phacoanaphylactic endophthalmitis, in which the patient is sensitive to lens protein. Certain of the plastics used in the manufacture of plastic eyes produce an allergic reaction, characterized by edema in the mucous membrane of the socket and a marked discharge.

Ralph W. Danielson.

Hoffman, R. S., and Messier, P. E. **Mechanism of corneal wound healing. I. Cells involved in corneal growth and repair.** Arch. Ophth. **42**:140-147, Aug., 1949.

A method is described for preserving rabbit corneal tissue in vitro indefinitely. A pattern of growth of corneal stromal cells was observed. This pattern includes a definite latent period before any growth is observed and a noticeable interchangeability in form of the stromal cells in response to changes in environment. The latent period of growth in the tissue cultures can be appreciably shortened by low-dosage irradiation, and the amount of growth can be increased by the addition of aqueous sheep heart extract. The cells obtained on culture of corneal tissue exhibit the characteristics of fibrocytes. Rapid freezing experiments on rabbit cornea in vivo were carried out. Corneal stroma cells are not specific for the cornea but may be derived by migration from adjacent fibrous tissues. After entering the cornea, these cells conform to the lamellar arrangement and assume the characteristics and functions of stroma cells.

John C. Long.

Messier, P. E., and Hoffman, R. S. **Mechanism of corneal graft healing. II. Behavior of recipient and donor cells.** Arch. Ophth. **42**:148-154, Aug., 1949.

Experiments carried on with corneal donor material grown in tissue culture, with frozen donor material and freezing experiments on the cornea in vivo showed that the cells in the donor cornea have no part in the healing of a corneal graft; rather, healing is the function of the cells of the recipient cornea. The maintenance of transparency of the graft depends on the rapid passage of the recipient cells into the donor tissue when devitalized donor material is used. With fresh donor material the viable cells in the donor are capable of carrying on metabolism in the donor tissue until they are replaced by the cells of the recipient cornea. A corneal graft should be classified as a replacement type graft.

John C. Long.

Negri, L., and Alajmo, A. **Retinal tumors and their histogenesis.** Giorn. ital. oftal. **2**:1-18, Jan.-Feb., 1949; **2**:89-90, Mar.-Apr., 1949.

Twelve cases of retinal tumor were examined both with the usual stains and the special glial staining of Bleu, Vittoria, Rizzo, and Cajal. There is still not sufficient evidence that retinal tumors in infants originate from glial elements. There are distinct differences in the histopathology of these tumors and the true retinal tumor observed in adults. The origin of these tumors from elements of the nervous cells and not from the epithelum is considered possible and for that reason the name of neuroblastoma is justified. Contrary to the majority of authors, Negri and Alajmo consider the rosettes as a special sign of immaturity.

Vito La Rocca.

Scheerer, R. **Eye diseases from the viewpoint of Ricker's causal relations theory.** Klin. Monatsbl. f. Augenh. **114**:412-419, 1949.

Ricker's theory tries to get away from the usual teleologic viewpoint of present day pathology. It looks for the more fundamental causal relations in pathologic reactions and regards the problem of blood circulation within the terminal vascular bed with its control through nervous impulses as the main point in pathology. Weak nervous impulses lead to a dilation of the vascular bed (fluxion), moderate impulses constrict arterioles and capillaries (anemia, ischemia) and strong impulses stop the excitability of constrictors and, somewhat later, also of vasodilators. The end result of the latter is "red stasis." Momentary reversible blur in vision is, according to the theory, the result of anemia following the constriction of the smaller retinal vessels. Retinal embolism can be explained by a phase of anemia followed by slight peristatic hyperemia and edema. In this it resembles a histamine shock. The edema is the result of the slowing of circulation. Thrombosis represents a higher degree of peristatic hyperemia. Such peristatic hyperemia is also found in the hypertonic fundus. (References.)

Max Hirschfelder.

Simonelli, M., and Esente, I. **Experimental diabetes from Allossana injections and its ocular manifestations.** Giorn. ital. oftal. 1:520-531, Nov.-Dec, 1948.

Through endovenous injections of Allossana in doses of 200 mgr. per kg. of body weight, a typical diabetic syndrome was started in six rabbits; four of these were killed 12 to 60 days later. Two died spontaneously after five and six months.

No ocular changes appeared in the first four animals; in the last two rabbits, some small cortical opacities appeared at the equator of the lens in the fourth month and slowly enlarged. Histologic examination of all six animals revealed typical pancreatic lesions and changes in the suprarenal and thyroid and the hypophysis. In the rabbit which survived six months, there was a progressive venous thrombosis in a small vessel of the pia of the optic nerve.

Vito La Rocca.

Weizenblatt, S. **Allergic ocular reaction to the tuberculin test; bilateral cyclitis and neuroretinitis.** Arch. Ophth. 41:436-443, April, 1949.

A healthy young white man with previously healthy eyes developed a bilateral neuroretinitis and cyclitis five days after a routine tuberculin test. The skin reaction was four plus. Eventually complete recovery occurred. Six and a half years later another tuberculin test was followed seven days later by a bilateral neuroretinitis and cyclitis. Complete recovery followed. There was freedom from ocular symptoms between the tuberculin tests. These ocular complications following injection of tuberculoprotein may be termed a delayed allergic reaction, such as is sometimes observed in serum disease. The literature of ocular hypersensitivity to tuberculin is reviewed.

John C. Long.

3

VEGETATIVE PHYSIOLOGY, BIOCHEMISTRY, PHARMACOLOGY, TOXICOLOGY

Cagianut, B., and Verrey, F. **The tracing of water metabolism in the human eye by the injection of heavy water into the anterior chamber.** Ann. d'ocul. 182:649-657, Sept., 1949.

Because of its easy identification, heavy water, D^2O, was employed to measure the rate of water transfer in the eye. From three human eyes to be enucleated because of choroidal sarcoma, approximately 0.2 cc. of aqueous was removed and replaced by the same quantity of heavy water immediately before enucleation. After enucleation the aqueous was withdrawn and placed in a sealed tube.

The lens and vitreous were similarly conserved. In approximately 2.7 minutes one half of the heavy water contained in the artificial aqueous was replaced by aqueous and in approximately 7 minutes entirely replaced. The authors' findings are similar to those of Kinsey, Grant, and Cogan in rabbits' eyes. Chas. A. Bahn.

Dorello, U. **Lysozymic action in the first and second aqueous.** Giorn. ital. oftal. **2**:43-51, Jan-Feb., 1949.

In man aqueous of first withdrawal is free from lysozimic action but is antilysozimic. In the second withdrawal it has lysozimic action and is thus more similar to the blood serum. In the ram, the aqueous of both the first and second withdrawals is free from lysozimic action and its antilysozimic activity is more marked in that of the second. Vito La Rocca.

Duane, T. D. **Metabolism of the cornea.** Arch. Ophth. **41**:736-749, June, 1949.

The literature on the respiratory activity of the cornea is reviewed. The relation of corneal respiration to the atmospheric environment is analyzed. The respiratory rates of the various corneal strata are collected, evaluated and recorded in tabular form. Evidence for the presence and operation of the various respiratory enzyme systems is discussed. The possible sources of nutrition for the cornea are reviewed. John C. Long.

Duke-Elder, S., Davson, H., and Maurice, D. M. **Studies on the intra-ocular fluids. 4. The dialysation of aqueous humor against plasma.** Brit. J. Ophth. **33**:593-601, Oct., 1949.

Results of studies on the dialysation of aqueous humor against plasma showed a decrease in the original concentration of chloride in the aqueous humor, and a rise in the corresponding concentration in the plasma. The results regarding sodium are equally consistent, but not so striking in magnitude. There was an increase in the resistance of the aqueous humor and a decrease in that of the plasma; the changes in conductivity were such as could be produced by a movement of sodium and chloride from the aqueous humor into the plasma. It was shown that the aqueous humor is not in thermodynamic equilibrium with the blood plasma so far as these two ions are concerned. Energy is expended in transferring sodium and chloride from the blood to the aqueous, that is, a process of secretion exists. The plasmoid aqueous humour formed after paracentesis is entirely different, and the ratio of the concentrations approximates unity. This indicates that during the rapid refilling of the anterior chamber the diffusible ions filter through the blood-aqueous barrier in amounts proportional to their concentrations in the plasma. There is thus no initial attempt to form a Donnan equilibrium. Orwyn H. Ellis.

Glees, M., and Wüstenberg, W. **Experiences with Mintacol in normal and glaucomatous eyes.** Klin. Monatsbl. f. Augenh. **114**:455-458, 1949.

The organic phosphorus preparation Mintacol differs from the American D.F.P., but seems to resemble it in pharmacological properties. It produces miosis for several days, strongly counteracts an atropinized pupil and induces accommodation. It does not lower a normal ocular tension, but lowers the pressure in glaucomatous eyes. The new drug is at least as good as pilocarpine or eserine in the treatment of glaucoma.

Max Hirschfelder.

Hart, W. M., and Chandler, B. F. **The cornea. I. Swelling properties of the fibrous tunic of the eye.** Arch. Ophth. **40**:601-611, Dec., 1948.

The swelling of isolated pieces of bovine cornea and sclera when immersed

in carefully prepared buffer solution was studied. It may be said that the behavior of the fibrous tunic of the eye in swelling is analogous to that of gelatin. The cornea and sclera are both lyophilic colloid systems and in general behave like such systems. The differences in behavior between cornea and sclera that are noted can be ascribed largely to differences in mechanical arrangement of the fibers. The presence of hyaluronosulfuric acid in the cornea and its absence from the sclera is a factor yet to be evaluated.

John C. Long.

Hart, W. M., and Chandler, B. F. **The cornea. II. Factors affecting the transmission of visible light by the fibrous tunic of the eye.** Arch. Ophth. **40**:612-623, Dec. 1948.

Determinations of transmissibility were made on bovine corneas placed in buffered solutions. Some of the corneas were opaque from ulcers or other causes. Drying caused these opacities to disappear and when these corneas were rehydrated, the opacities did not reappear. The transmission and diffusion of light by the cornea are subject to the same chemical and mechanical influences as those which have been found for gelatin. Similarly, the anisotropy of the cornea is a function of its fibrous structure and the lamellar arrangement. Its greatest swelling is at right angles to the direction of its fibers. The arrangement of the collagenous fibers in the fibrous tunic of the eye is believed to be fundamental in determining the optical difference between cornea and sclera. John C. Long.

Martinetti, R., and Rubino, A. **Arterial retinal pressure in experimental headache.** Giorn. ital. oftal. **1**:498-504, Nov.-Dec., 1948.

The authors studied the behavior of arterial retinal pressure in experimental headache caused by histamin and trinitrin.

While histaminic headache is associated with a slight increase in the diastolic pressure in the retinal arterioles, that of trinitrin is hardly noticeable. Vito La Rocca.

Pasca, G. **A new anesthetic, farmocain, and the mydriatic action of cocaine substitutes.** Boll. d'ocul. **28**:289-304, May, 1949.

Farmocain is para-butylamino-benzoil-diethylamino-ethanol chloride and proved a satisfactory surface anesthetic in ½ and even in ¼-percent solutions. It was also used for cataract extraction in combination with adrenaline; without the latter it causes a mild conjunctival hyperemia. One half-percent solutions do not harm the corneal epithelium; the one-percent solution, however, does, Repeated instillation of solutions higher than ¼-percent produce mydriasis. Intraocular pressure was not influenced. Novocain, tutocain and pantocain also produced mydriasis when applied in the usual concentrations. Butocain had no mydriatic effect when used alone. Percain never dilated the pupil even when combined with adrenaline. The mydriatic effect of all anesthetics is variable and depends mainly on the age of the patient. (7 tables.) K. W. Ascher.

Ratschow, M. **The normal and pathologic physiology of the circulation in the smallest vessels.** Klin. Monatsbl. f. Augenh. **114**:481-496, 1949.

In this article for postgraduate education the structure and the function of the smaller arterioles, capillaries and venules are described and the nervous and humoral regulators which are involved in this system in a reciprocal manner are set forth. Clinical methods of examination by direct microscopy of the capillaries and indirect functional tests are described. Pathologic processes in the terminal capillaries in vasomotor instability, Raynaud's

disease, endangiitis obliterans and also capillary fragility and permeability are discussed. Max Hirschfelder.

Thiel, H. L. **Experiments with a new synthetic miotic drug "Mintacol" in glaucoma.** Klin. Monatsbl. f. Augenh. **114**:454-455, 1949.

A new synthetic organic phosphorus preparation, Mintacol, produces a strong miosis and proved useful in chronic and acute glaucoma. A 1 to 7,000 aqueous solution is recommended.

Max Hirschfelder.

Winkelman, J. E. **The motor impulse elicited by the retinal stimulus and the binocular optical reflexes.** Brit. J. Ophth. **33**:629-635, Oct., 1949.

These experiments concern fusion and movement in the horizontal direction. Similar studies made with the stimuli placed vertically gave corresponding results. It is seen that each retinal stimulus gives rise to both a sensory and a motor impulse. The latter is responsible for movements of the eyes to one side and also movements of the eyes in opposite directions. These movements produce localization in space and the perception of apparent movement. Fusion, localization and perception of apparent movement are physiologic rather than psychologic phenomena. Orwyn H. Ellis.

4

PHYSIOLOGIC OPTICS, REFRACTION, COLOR VISION

Albrich, K. **Aniseiconia from a clinician's point of view.** Klin. Monatsbl. f. Augenh. **114**:420-428, 1949.

The author describes a simple instrument which permits the direct comparison of image size in both eyes during central fixation. Aniseiconia can be found frequently, but only rarely gives clinical symptoms. It may be of importance in the origin of strabismus. One should not make a diagnosis of aniseiconia unless the symptoms disappear after occlusion of one eye (monocular test).

Max Hirschfelder.

Berens, C. **Modified three character test for binocular vision, especially applicable to the examination of amblyopic children.** Arch. Ophth. **41**:460-461, April, 1949.

The test object consists of a figure of a child which transmits red lights, an elephant which transmits green light and a white ball with a red and a green square in the center. A red glass is worn before the right eye and a green glass before the left. If the patient is able to make out the red child, the green elephant and the white ball with the red and green squares, he has at least first grade binocular vision. The figures are large enough for most amblyopic patients and the characters are usually recognized by children from three to four years of age.

John C. Long.

Bonavolonta, G. **The behavior of light perception in the course of experimental hypoglycemia.** Giorn. ital. oftal. **1**:505-519, Nov.-Dec., 1948.

The author studied the behavior of light perception in nine healthy subjects with hypoglycemia provoked by insulin injections. In seven there was a marked decrease of the ability to see light in darkness which can be attributed to the fleeting change in the glycolysis in the retina. Vito La Rocca.

Diaz-Caneja, Emilio. **A second contribution to the study of binocular alternation.** Arch. Soc. oftal. hispano-am. **9**:475-500, May, 1949.

This is an extensive review of the literature, including the author's first contribution in 1928, in which he demonstrated an alternation in function and suggested an association of the super-

ficial layers of both cortical areas and an inhibition of the deeper layers. The results of this second study indicate that the anatomic pattern of the cortical visual areas does not determine the act of visual perception, and that this complicated process does not lend itself to a rigid anatomic localization. (6 figures in color.)

Ray K. Daily.

Eggers, H. **Reserve accommodation.** Arch. Ophth. **41**:701-703, June, 1949.

Weakness of the accommodation is a frequent cause of asthenopia and should be tested for during refraction. Reserve accommodation may be measured by asking the subject to read aloud at 11 inches while wearing his distance correction. Progressively stronger minus spheres are inserted in the trial frame until the patient falters in the reading. The diopteric power of the spheres that just failed to produce faltering is a measure of the reserve accommodation.

John C. Long.

Engelbrecht, Kurt. **Twilight myopia in hypermetropes.** Klin. Monatsbl. f. Augenh. **114**:543-548, 1949.

The theoretical differences between twilight myopia and night myopia are discussed. The former is caused by chromatic aberration because the more refractile short waves alone of the visible spectrum are visible in twilight. The latter is based on "remote point accommodation" during daylight and complete relaxation to a position of rest during darkness.

Max Hirschfelder.

Katz, Joachim. **Color glare.** Klin. Monatsbl. f. Augenh. **114**:548-556, 1949.

Recognition can be materially reduced by glare. The blinding effect of the various colors of the spectrum varies. Katz subjected the eyes of test persons to glare of various monochromatic colors and then checked their visual acuity. It was found that orange colored light of a wave length of about 6400 Å has the least blinding effect and that the recognition of objects is considerably better with orange light than dark red. The author distinguishes two types of blinding effect. One is the effect of sudden increase of light on the retina which disturbs the photochemical changes of adaptation. The other is a disturbance of the act of seeing in the cortex of the brain or a "central or psychologic blinding." The latter can be investigated by exposing only one eye to the colored glare, while checking the other eye with test objects. The results of the author's investigations are of practical importance for traffic illumination and for military purposes.

Max Hirschfelder.

Polliot. **Binocular problem.** Ann. d'ocul. **182**:686-701, Sept., 1949.

This contribution is largely devoted to the discussion of a previous article on this subject by Plicque, which was abstracted in this journal. The existence of a physiologic horopter coördinating the special relations of the retina binocularly is assumed. Several experiments are mentioned illustrating the relationships of the conscious and unconscious as well as the objective and abstract in the establishment and maintenance of binocular single vision.

Chas. A. Bahn.

Urrets Zavalia, Alberto, Senior and Junior. **Myopia and vitamin D.** Arq. brasil. de oftal. **12**:62-76, 1949.

Forty patients were given high doses of vitamin D. After an average lapse of one year the myopia had not undergone significant statistical modification. The author conjectures that the result may suggest but does not prove the idea that vitamin D really possesses the quality attributed to it by Knapp.

W. H. Crisp.

Wagner, Eberhard. **The time threshold of depth perception.** Klin. Monatsbl. f. Augenh. **114**:557-562, 1949.

It requires more time to perceive the impression of depth than to recognize the objects involved in the act of sight. The author experimented with test persons who viewed two movable needles. The threshold at which depth between the two needles could be observed was determined in experiments, in which no time factor played a part. Then the minimum time required for the recognition of the depth threshold was ascertained. The curves for the time threshold in various distances formed an analogue to the curves found in electric stimulation of nerves. The test persons needed from 1/3 to 1/7 of a second to recognize their minimum threshold. The double value of the depth threshold (chronaxy) varied from 1/5 to 1/14 of a second of observation time. Max Hirschfelder.

Wold, K. C. **Hereditary myopia.** Arch. Ophth. **42**:225-237, Sept., 1949.

The author reviews the literature on the types and etiology of myopia. Prescription of glasses with consideration of accommodative power, muscle balance, age and occupation is the best treatment for hereditary myopia. Illumination, position of the head in reading, outdoor recreation, well balanced diet and choice of occupation are important. All treatment such as stimulation of the ciliary muscle, administration of calcium for the sclera, of thyroid for correction of low metabolic rate and of medication for choroiditis cannot alter the hereditary pattern and is futile. Hereditary myopia may be dominant, recessive, or sex linked.

For acquired myopia, the result of disease or trauma, ordinary or contact lenses, cataract extraction, penicillin therapy, local treatment of the eyes or insulin is indicated.

Myopia was found in 2.7 percent of newborn infants under 7 days of age and in 6.5 percent of all children under 6 years of age. In a survey of 257 kindred with myopia, 230 of 645 children of nonmyopic parents, or 35 percent, were myopic, and 309 of 628 children with one or two myopic parents, or 49 percent, were myopic. Ralph W. Danielson.

5

DIAGNOSIS AND THERAPY

Arruga, H. **The relative importance of direct and indirect ophthalmoscopic examination in the treatment of retinal detachment.** Brit. J. Ophth. **33**:651-653, Oct., 1949.

The relative importance of using both direct and indirect ophthalmoscopic examination in retinal detachment is enumerated. It is pointed out that while direct ophthalmoscopy is excellent for differential diagnosis of hemorrhages and measurement of retinal level, indirect ophthalmoscopy has a larger field and better view of the periphery and intense illumination can be employed. (6 figures on color plate.) Orwyn H. Ellis.

Azzolini, U. **Filatov tissue therapy in ophthalmology.** Giorn. ital. oftal. **2**:59-63, Jan.-Feb., 1949.

In three patients with high myopia, in four with retinitis pigmentosa, and in six with old leukoma, subconjunctival transplants of placenta were performed and 20 injections of aqueous extract of placenta were given. In the myopic patients there was a slight and temporary improvement of vision; in the retinitis pigmentosa there was no improvement at all, and in leukoma improvement was fair. More experiments were made with negative results in the application of erythrocyte powder in cases of corneal ulcers.

Vito La Rocca.

Bock, R. H. **A new instrument for obtaining lamellar grafts.** Arch. d'opht. 9:458-462, 1949.

Bock describes a simple instrument which facilitates the obtaining of partial or total lamellar grafts. It consists in the application to the cornea of the Tiersch graft technique by which the cornea is flattened before the blade of a knife. The grafts are regular, and traumatism minimal. The technique is described in detail and special attention is called to the importance in partial grafts of not confusing the two surfaces. The graft is placed between two watch glasses with the epithelial surface down. Total grafts maintain their normal corneal curvature so that no confusion of surfaces is possible. (10 photographs.) Phillips Thygeson.

Chamlin, Max. **Minimal defects in visual field studies.** Arch. Ophth. **42**:126-139, Aug., 1949.

The author uses the 1/300 test object for study of the peripheral fields and the 1/2,000 test object for study of the central fields. Three criteria are presented, with clinical examples, for detecting minimal filed defects, namely level differences, rapid comparisons for qualitative differences, and breadth of field. Methods of eliciting level differences and of carrying out rapid comparisons are described. In neurological cases the perimetrist's minimal field findings must be corroborated by roentgenography, air studies, electroencephalography and angiography.

John C. Long.

Curry, J. J., and Shaw, E. A. **Continuous intravenous injection of typhoid vaccine in treatment of certain ophthalmic diseases.** Arch. Ophth. **42**:123-125, Aug., 1949.

An isontonic sodium chloride solution containing 1,000,000,000 killed typhoid organisms per litter is injected intravenously at the rate of 20 to 30 drops per minute for 4 to 12 hours. Rectal temperatures are recorded each 15 minutes. The degree of reaction is controlled by the rate of flow. The general condition of the patient and the severity of the disease treated are considered in regulating the duration and severity of the reaction. If sufficient improvement does not occur from one treatment, a second continuous injection is given within 48 hours. A total of 17 patients with ophthalmic diseases, including non-specific iritis, syphilitic keratitis and suspected sympathetic ophthalmia, were treated in this manner, with gratifying results in every case. This method of treatment is recommended because it may be given safely to elderly and debilitated patients and the degree of fever and chilling may be controlled.

John C. Long.

François, P. **Slower absorbing penicillin in ophthalmology.** Ann. d'ocul. **182**:702-705, Sept., 1949.

Among the disadvantages of the more rapid acting penicillin preparations are renal blockage, drug accumulation at the site of injection, and local vasomotor constriction. Two types of penicillin preparations with a slower rate of absorption are advised. In the first type, cholesterol in oil (subtosan) and phenoxetol (solvent P) are employed. These maintain the penicillin level in the blood for approximately 24 hours. In the second and more prolonged type, peanut oil and peniquinyl extend the drug action from 24 to 48 hours. For long instillation, calcium penicillin in a solution of monophosphate and bi-potassic-formaldehyde is suggested because it is nonirritating and can be preserved without diminished efficiency for about twelve days at room temperature. If penicillin is indicated in anterior internal ocular infections, 200,000 units of penicillin in sustosan is advised subcon-

junctivally with scleral scarification. The intraocular injections of slower absorbing penicillin preparations in human eyes is experimental. Chas. A. Bahn.

Houssin, J. **Research on the light sense with the aid of the Haas photoptometer.** Arch. d'opht. **9**:331-335, 1949.

Houssin studied the light sense in a variey of pathologic conditions by means of the Haas photoptometer. Three thresholds were obtained, as follows: 1. the base threshold at which light was first recognized; 2. the differential threshold at which the Landolt ring was recognized but the opening in the ring not determined; and 3. the threshold of visual acuity at which the opening of the Landolt ring was seen. Three minutes were allowed for adaptation time. The author explains her variation from standard procedure as an effort to obtain a simple technique adaptable to routine office use.

In hypermetropia and hyperopic astigmatism she found no variation from the normal figures, but in myopia and myopic astigmatism she found the differential and visual acuity thresholds increased according to the extent of myopic chorioretinal degeneration. In primary optic atrophy the first two thresholds were markedly elevated and the visual acuity threshold impossible to measure even though in strong light an acuity as high as 5/10 could be demonstrated. In optic atrophy secondary to a papilledema, all three thresholds were only slightly elevated. In contrast, optic neuritis produced a major elevation in all three thresholds, particularly in the first. In retrobulbar neuritis there was principally an elevation of the second and third thresholds, a finding which was valuable in the diagnosis of multiple sclerosis. In retinitis and chorioretinitis involving the macula, only the visual acuity threshold was altered. In retinal detachment after successful operation and restoration of normal vision, there was still a notable elevation of all three thresholds. In incipient glaucoma there was an elevation of the base threshold and the visual acuity threshold. The author concludes that the method may prove to be useful in diagnosing and following the evolution of numerous ophthalmologic conditions.

Phillips Thygeson.

Iribarren, F., and Iribarren, R. **The Pérez Llorca suction disc for cataract extraction.** Arch. de oftal. d. Buenos Aires **23**:372-374, Nov.-Dec., 1948.

This simple suction apparatus consists of two parts, a metallic tube terminating in a suction-cup 5 mm. in diameter and 1½ mm. high, and a small rubber bulb which receives one end of the metallic tube and which is grasped between the thumb and next two finger-tips. The corneal section must be somewhat larger than usual to allow the introduction of the metal tube and tip. This latter is placed on the anterior lens surface after the rubber bulb has been pinched to expel its air. The bulb is now allowed to resume its normal size and the negative pressure resulting at the junction of the tip and lens facilitates the simple intracapsular extraction. The instrument closely resembles the Bell erisiphake manufactured by Storz Surgical Instruments. (1 figure.) Edward Saskin.

Jébéjian, Robert. **Tissue therapy in numerous ocular affections.** Ann. d'ocul. **182**:658-671, Sept., 1949.

Masses of specially prepared placenta were implanted under the ocular conjunctiva. The placenta was preserved one week at 2 to 4 degrees C., then autoclaved at 120 degrees for one hour, and finally preserved at 2 to 4 degrees C. for 1 to 2 days before use. The treatment was used successfully in 78 patients with a wide

variety of lesions. The author suggests further experimental use to determine its limitations. Chas. A. Bahn.

Kapuscinski, W. J. **The influence of typhoid vaccine on the reticuloendothelial systems in uveitis.** Arch. d'opht. 9:201-207, 1949.

Kapuscinski refers to a previous communication in which he described a provocative test with typhoid vaccine which aided in the differential diagnosis between uveitis of tuberculous origin and that due to focal infection. He employs the vaccine for treatment in non-tuberculous cases only and describes almost constantly favorable results, even in cases in which removal of the exciting focus was impossible. In considering the possible methods of action of the vaccine he notes that local hyperthermia never gives the therapeutic effect of the fever produced by the vaccine. He considers that fever alone could not account for the effect and that stimulation of the reticulo-endothelial system must play an important part. For the purpose of studying this effect he analyzed the cytologic formula of the aqueous humor and of the blood before and after typhoid vaccine injections. In the majority of cases he noted a blood monocytosis and in the aqueous an increase in the number of histocytes. He concludes that the vaccine probably has a therapeutic effect on the primary focal infection as well as on the eye itself.

Phillips Thygeson.

Nižetič, B. Z. **Thyrothricin in ophthalmology.** Boll. d'ocul. 28:257-266, May, 1949.

Sixty-three patients with such different eye diseases as conjunctivitis, blepharitis, dacryocystitis, keratitis, serpiginous ulcer, keratoconjunctivitis were treated with thyrothricin. The results are described as "rather poor" but Nižetič concedes the usefulness of thyrothricin in lingering diseases and in patients with sensitivity to other antibiotics. Thyrothricin does not produce bacterial resistance or allergic reactions. In rabbits, the drug failed to act on infections with herpes virus. For treatment of patients, it was used by instillation or by touching of circumscribed lesions. K. W. Ascher.

Tower, P. **Contact lens electrode for iontophoresis.** Arch. Ophth. 41:730-733, June, 1949.

The electrode for iontophoresis consisted of two contact lenses which are fused together and have a four-pronged platinum electrode between them. Four holes are drilled into the limbal portion of the inner lens. The danger of corneal injury is eliminated by preventing contact with the metal electrode. This electrode will stay in place without further support by the operator. (2 figures.)

John C. Long.

6

OCULAR MOTILITY

Arriaga Cantullera, José. **Paralysis of convergence.** Arch. Soc. oftal. hispano-am. 9:620-647, June, 1949.

The literature on the physiology and the anatomical basis of convergence is thoroughly reviewed, and cases illustrating disturbances in this function are reported. It is pointed out that it is necessary to differentiate true paralysis of convergence, from lack of convergence in divergent strabismus; the latter is due to the absence of fusion impulses, rooted in a low visual acuity of the deviating eye.

Three cases are reported to illustrate true disturbances of convergence, which spring from lesions in the reflex arc which controlls this function. In two patients there was paralysis of voluntary convergence, and in one of all convergence. In

the two cases in which only voluntary convergence was paralyzed the patients were unable to converge when asked to look at the tip of their nose, but the eyes followed a finger approaching the eyes at the midline. In one patient, 55 years old, this was associated with a paralysis of the right inferior rectus, and was attributed to vascular spasm in the cerebral arteries. In the other patient, 21 years old, the paralysis of voluntary convergence is considered a sequel of encephalitis in childhood. The patient with complete convergence paralysis had a luetic oculomotor paralysis of one eye and recovered completely. (6 figures.) Ray K. Daily.

Luz, Barbosa da. **Visual reëducation of the strabismic.** Rev. brasil. de oftal. **8**:41-58, 1949.

With statistical tables and three illustrations, the author analyses the results obtained by visual education, alone or in combination with surgery, in 143 cases of strabismus treated in the orthoptic department of the Paulo Filho clinic. Of the patients whose cases are recorded here, 44.7 percent discontinued or interrupted the treatment. Of the 63 patients who completed the treatment, 24 showed perfect binocular vision, 5 had perfect binocular vision but needed to wear glasses, 21 had parallel visual axes and good appearance but deficient binocular vision, 7 had good binocular vision with the synoptophore but occasional defiiciency with ordinary use of the eyes, 2 had a slight postoperative angle of defect, and 4 persisted in the deviation. W. H. Crisp.

Marquez, M. **Supposed torsion of the eye around the visual axis in oblique directions of gaze.** Arch. Ophth. **41**:704-717, June, 1949.

The experiments of Ruete showed that the after-image of a bright vertical cross when projected obliquely on a vertical wall had acute angles. This was erroneously ascribed by Donders and by von Helmholtz to a movement of torsion or of rotation around the visual axis. The author has shown the mechanism which produces the obliquity of the after-image by new experiments and clarified them with diagrams. Normally there are no torsional movements for the purpose of aiding vision and those movements which appear as torsion are in reality pseudotorsions produced by rotation around an oblique axis in Listing's plane. John C. Long.

7

CONJUNCTIVA, CORNEA, SCLERA

Barski, G., Grom, E., and Croissant, O. **Study of trachoma with the aid of tissue culture and the electron microscope.** Arch. d'opht. **9**:321-330, 1949.

These workers from the Pasteur Institute and the ophthalmologic clinic of the Hotel-Dieu, Paris, studied material from ten cases of active trachoma of from four months to five years duration. They were unable to demonstrate free elementary or rickettsioid bodies but found Halbertstaedter-Prowaezk inclusion bodies both in the original tissue and in inoculated human embryonic conjunctiva grown in tissue culture. The inclusions were much more numerous in tissue culture than in the original trachomatous material. The electron microscope failed to reveal additional significant findings.

Phillips Thygeson.

Cogan, D. G. **Vascularization of the cornea: its experimental induction by small lesions and a new theory of its pathogenesis.** Arch. Ophth. **41**:406-416, April, 1949.

After the production of small experimental lesions in the rabbit cornea, a sequence of events leading to new vessel formation occurred with remarkable regularity. After a latent period there was engorgement of the proximal venules and

capillaries and the formation of saccular aneurysms on their walls. These aneurysms burst and caused hemorrhage into the corneal stroma and prompt deflation of the vessels. The hemorrhagic area then became riddled with new capillaries, most of which receded in the course of a few days, leaving a few loops directed toward the lesion. The one event which appeared to be correlated with, or to precede, the vascular changes was swelling of the corneal stroma. It is held that the engorgement of the vessels, the formation and ultimate bursting of the saccular aneurysms and other events leading to interstitial vascularization of the cornea are due to reduction in the tissue compactness of the cornea in the region of preexisting vessels. John C. Long.

Gogan, D. G., Albright, F., and Bartter, F. C. **Hypercalcemia and band keratopathy.** Arch. Ophth. **40**:624-638, Dec., 1948.

Band keratitis and calcification of the conjunctiva is reported in 18 cases of hypercalcemia and in another in which the calcium level of the blood may be presumed to have been elevated previously. The hypercalcemia was due to hyperparathyroidism in four, to vitamin D poisoning in five and to sarcoidosis in two. In the remaining eight it was associated with severe renal damage, owing, in some cases, to a high calcium and high alkali intake. The corneal change consisted of paralimbal opacification extending two to three mm. axialward in the palpebral fissure. Many of the patients had nephrocalcinosis or nephrolithiasis, and the process in the kidneys was thought to be analogous to that in the cornea. John C. Long.

Coppez, L. M. **A technical and physiopathologic study on ten cases of partial lamellary keratoplasty.** Bull. Acad. roy. de méd. de Belgique **14**:313-324, 1949.

Partial lamellary keratoplasty, not as widely used as the partial perforating keratoplasty, seems to have so many advantages that in the future it might well be the operation of choice. The visual results are excellent in spite of an irregular astigmatism as long as the dissection of the central part of the transplant is done with certain precautions. It should not be larger than 6 mm. and only the exact center of the dissected part should reach Descemet's membrane. The borders should be thinner so that the future transplant will rest on a thick layer of the host's cornea. This gives good central transparency, reduces the central astigmatism and yet provides a better nutrition and position of the transplant. This operation may be done on an inflammed eye and the surgical risks are less than in the perforating variety. Since the anterior chamber is not opened there are no complications like iritis, glaucoma or anterior synechias. The technique of this operation is very delicate and requires the utmost care in handling of the host cornea and of the transplant. The author describes the procedure in detail and summarizes his personal experiences in ten case histories. (*2* figures.)

Alice R. Deutsch.

Desvignes, P. **Descemetitis.** Arch. d'opht. **9**:340-346, 1949.

Desvignes states that the term descemetitis implies an actual inflammation of Descemet's membrane and differs from the keratitis punctata of uveitis although the two may co-exist. Descemetitis, although little mentioned in modern textbooks, is not a rare condition. Three types occur. The first is a traumatic descemetitis occurring after operative or other trauma and healing in a few days. The second is an inflammatory descemetitis which can occur as a primary condition or associated with an iridocyclitis or keratitis and which has the same clinical signifi-

cance as a uveitis. It heals most often with some interstitial scarring. The third is a trophic descemetitis without inflammatory phenomena which results in a chronic edema of the cornea and has a poor prognosis. The author concludes that Descemet's membrane possesses a pathology of its own and that when it becomes involved, modification of the transparency of other layers of the cornea always occurs.

Phillips Thygeson.

Diaz-Domínguez, D., and Hernández Arrieta, M. **Primary anesthetic edema of the cornea.** Arch. Soc. oftal. hispano-am. **9**:577-595, June, 1949.

The authors illustrate with case reports the various corneal lesions characterized by diminished corneal sensitivity, such as diffuse superficial keratitis, neuroparalytic keratitis following alcohol injection into the Gasserian ganglion, Fuchs's epithelial dystrophy, Birnbacher's keratitis with myotonic dystrophy, primary corneal edema of Paufique, Chavanne and Prost, Aubineau's corneal edema of hypercholesterinemia, keratitis due to cold, and symmetrical dystrophy of Crespi. These affections differ mostly in intensity. They can be all called primary anesthetic edema of the cornea. Although a lesion of the corneal nerves is the basis of these lesions, there must be another factor otherwise bullous keratitis would follow every ocular operation, and there would always be neuroparalytic keratitis after alcohol injection into the Gasserian ganglion. This other factor, the author believes, is a disturbance of the amino-acid metabolism. In his patients amino acid therapy was followed by surprisingly favorable results.

Ray K. Daily.

Di Ferdinando, R. **The surgical treatment of pterigium using the method of A. Tersan in conjunctival autoplasty.** Giorn. ital. oftal. **1**:543-551, Nov.-Dec., 1948.

The author ascribes the success of such plastic surgery to the fact that in rebuilding the limbus, after the removal of the pterigium, a tissue of different structure is used which does not react with hyperplasia to microtrauma.

Vito La Rocca.

Djacos, Constantin. **Ocular disturbances in the deficiency edemas.** Arch. d'opht. **9**:421-426, 1949.

Djacos calls attention to the tragedy of the Greek people during the occupation. The deficiency edemas first started in November, 1941 and during the winter months became widespread in the population. During this time the daily caloric content of the diet distributed to the people of Athens varied from a high of 510 in September to a low of 204 in February. The author was able to examine 107 among the many dying from hunger on the streets and brought into the State General Hospital. The eyes of the patients, while grossly negative, showed on slit-lamp examination special corneal lesions stainable with fluorescien which the author describes under the name "superficial polymorphous keratopathy."

Djacos describes three forms of this keratopathy. The first, encountered in mild forms of deficiency edema, is characterized by numerous small round, oval, or bacillary staining spots which in optical section are seen to be intra- or subepithelial but which do not involve Bowman's membrane. The second, seen in more severe cases, is called the hydropic form and is characterized by larger spots surrounded by halos. The third form is that of ulceration, seen only in very severe cases. In optical section the ulceration is seen to involve the epithelium only. In all forms the remainder of the cornea continued to be normal, except that in the periphery in rare cases interstitial lesions of important dimensions were seen.

In the 107 cases studied the author found no other significant eye lesions but he calls attention to the reports of Spyratos and Petzetakis and of Sphallangacou-Tranou and Velissaropoulos, all of whom described edema of the retina. (Colored plate.) Phillips Thygeson.

Klein, M., and Miller, S. J. H. **Local application of urea for the treatment of dendritic ulcer.** Brit. J. Ophth. **33**:643-651, Oct., 1949.

Hypertonic (25 percent) solutions of urea applied locally to an eye-bath are found to favorably influence the healing of dendritic and marginal corneal ulcers. Solutions must be both fresh and sterile to be effective. The healing time of recurrent dendritic ulcers is always of long duration but is considerably shorter if the ulcer develops on corneal scars of other than dendritic origin. After the urea treatment, protection of the healed cornea with a mild lubricating ointment helped to prevent relapses. Improvement in general health was found to be important for prompt healing. Orwyn H. Ellis.

Portugal de Souza, Ovidio. **Serious eye phenomena produced by collyria with trypoflavin base.** Rev. brasil. de oftal. **8**:31-39, 1949.

Many cases of catarrhal conjunctivitis are seen in the area of high Sorocabana and north of the Paraná, Brazil, of greater severity during the months from December to April. Of a commercial remedy much used there for the relief of the local irritation, an important constituent is trypoflavin or acriflavin. The author gives brief case histories of conjunctival and corneal complications in 18 patients who had been self-treated with this preparation. The results seem to have been more or less benign as regards any possible drug action, although there is apparently some suggestion of a need for closer therapeutic control of these patients.
W. H. Crisp.

Romero, E. **A mixture of fluorescein and mercurochrome in the treatment of corneal lesions.** Arch. Soc. oftal. hispano-am. **9**:670-672, June, 1949.

The author advocates a mixture of 2-percent fluorescein and 4-percent mercurochrome for staining as well as for therapy. Mercurochrome is a powerful penetrating antiseptic and fluorescein alleviates the irritation of mercurochrome, and has a beneficial action on local asphyxia. Mercurochrome stains the areas denuded of epithelium, and fluorescein outlines their borders, and stains still adherent diseased epithelium. (2 figures.)
Ray K. Daily.

Sacks-Wilner, E. P., and Sacks-Wilner, A. **Penicillin as a prophylactic against ophthalmia neonatorum.** Arch. Ophth. **41**:444-449, April, 1949.

A comprehensive study of the conjunctival flora was made on 251 newborn infants. Immediately after birth a conjunctival smear was taken of each eye and two or three drops of penicillin solution (5,000 units per cc.) was instilled. Twenty-four hours later another smear was made and a third was taken before discharge from the hospital. Gonococcic ophthalmia is relatively rare in newborn infants. It may be that if the mother has had proper prenatal care, the newborn infant needs no therapy other than irrigation of the conjunctival sac with an isotonic saline solution. It is recommended that infants whose mothers have not received proper prenatal care receive an immediate instillation of any antiseptic which is capable of rendering harmless the gonococcus or gram-positive organisms. In the experience of the authors a solution of penicillin is both prophylactic and therapeutic. It presents many advan-

tages in that it is effective, nonirritating and harmless to the eye. John C. Long.

Sorsby, A., and Kane, I. **Optimal methods in the treatment of ophthalmia neonatorum.** Brit. M. J., pp. 562-565, Sept. 10, 1949.

In 151 cases of ophthalmia neonatorum several different methods of treatment were used. Oral administration of doses of 200,000 units of penicillin either above or after an intial intramuscular injection proved disappointing. Combined oral sulphonamide and local penicillin therapy proved effective in reducing the duration of treatment but ineffective in reducing the considerable frequency of relapses seen with either sulphonamide or penicillin therapy. Duration of treatment was likewise reduced by increasing the dose of sulphonamide. With sulphamezathine, 0.5 g. initially and a maintenance dose of 0.25 g. every six hours, some seventy percent of cases showed clinical cure within 1 to 3 days. Similar results were obtained with sulphamerazine, 0.5 g. initially and 0.25 g. at 8-hour intervals. The use of larger doses of sulphonamide does not apparently influence the relapse rate; it is, however, possible that sulphamerazine may prove to be a favorable exception. For the present the best way of administering penicillin is still the instillation of drops of 10,000 units per ml. initially at intervals of a minute for one half hour and subsequently at less frequent intervals. For the best results with sulphonamide therapy higher doses than those used previously are necessary.

Theodore M. Shapira.

Stansbury, F. C. **Circular corneal transplants; surgical technique; instruments and sutures; comparison with the use of square transplants.** Arch. Ophth. **42**:155-169, Aug., 1949.

A simplified, surgical procedure for use of circular, penetrating corneal transplants is described in considerable detail. Various types of corneal trephines are discussed and evaluated. The author recommends the simple, manual, Elliott type of instrument. A simple method of suturing the graft in place is presented and is compared with the single, continuous suture. The use of additional corneal sutures in bulging grafts is mentioned. The circular type of corneal transplant is compared with the square type. The circular graft is easier to manipulate and with it eyes see and look better. John C. Long.

Strazzi, A. **Roentgen therapy of corneal diseases.** Boll. d'ocul. **28**:267-272, May, 1949.

In 770 cases corneal disease was successfully treated with X-rays, using 5 to 6 applications of 60 to 80 r at 5 to 6 day intervals. Use of Roentgen therapy is advised for interstitial, deep, sclerosing keratitis, phlyctenular and herpetic, hypopyon keratitis if not too severe, corneal abscess, and in protracted cases of corneal ulcer. K. W. Ascher.

Trevor-Roper, P. D. **Hyaline membranes on the posterior corneal surface.** Brit. J. Ophth. **33**:635-643, Oct., 1949.

Three case reports of hyaline membranes on the posterior corneal surface are presented. In the congenital form an incomplete separation of the membranous pupillary membrane from the endothelium may occur producing an anterior synechia of pupillary membrane, and secondarily, of iris to endothelium. This produces a stripping off of the endothelium may occur, producing an anterior cornea by traction of the synechia. Underdevelopment of the anterior segment was noted, as is often present with persistent embryonic tissues. Similar congenital membranes may result from intra-uterine inflammation. Hyaline membranes may result from birth trauma caused by pressure directly on the cornea by the

long axis of the forceps blade, everting and vertically splitting the inner layers producing a falciform or segmental detachment of Descemet's membrane. Fine powdery opacity in the substantia propria of the area that has been denuded is typical of severe damage where fibrosis has followed the initial edema. High astigmatism is present in the axis of the tear. Inflammatory retrocorneal membranes may occur in syphilitic interstitial keratitis or other forms of intense uveokeratitis. They are seen as irregular fibrinous lamellae, reticulate or stellate, of varying thickness and density. Initially they are probably wholly in contact with the endothelium, but become detached when their fibrin content retracts. Orwyn H. Ellis.

Vila Ortiz, J. M., Decoud, A. C., and Granados, E. **Histopathologic considerations of conjunctival alterations clinically classified as pingueculas.** Arch. de oftal. d. Buenos Aires **23**:329-334, Nov.-Dec., 1948.

These conjunctival alterations are primarily characterized by collagenous hyaline degeneration and elastic degeneration. Secondarily are found colloidal degeneration, calcareous deposits, vascular congestion and edema, and epithelial atrophy or hypertrophy. Grossly, there may be a more or less demarcated yellow color, or a white appearance due to local sclerosis and degeneration, or a more or less red hue due to vascular congestion. This study is to be continued. (6 photomicrographs.) Edward Saskin.

8

UVEA, SYMPATHETIC DISEASE, AQUEOUS

Adamantiadis, B. **Recurrent anterior segmentitis.** Arch. d'opht. **9**:336-339, 1949.

In the French literature the term "segmentite anterieure" is used to designate the simultaneous or successive involvement of two or more membranes of the anterior segment of the eye. Adamantiadis reports the case of a man, 55 years old, with a history of recurrent attacks of acute iritis and deep keratitis, of great severity but of short duration. The attacks involved both eyes but not simultaneously, and recurred at progressively shorter intervals. The author considered two diagnostic possibilities: 1. recurrent iritis with hypopyon, and 2. allergic uveitis. In view of the absence of hypopyon and of skin or mucous membrane lesions, the former possibility was discarded and an allergic etiology considered most likely. Phillips Thygeson.

Brennan, A. J., Brown, T. McP., Warren, J., and Vranian, G. **A. syndrome characterized by generalized cutaneous eruption, chorioretinitis and eosinophilia, probably due to chronic toxoplasma infection.** Am. J. Medicine **7**:431-536, Sept., 1949.

It is the purpose of this paper to describe a heretofore unreported type of chronic illness characterized by the presence of a generalized cutaneous eruption, chorioretinitis and eosinophilia of three years' duration. Serologic tests and an intradermal skin test for toxoplasmosis were strongly positive. Sulphonamide therapy was beneficial but the appearance of hematuria necessitated discontinuance of the drug. After this the patient's condition deteriorated. The possible etiology is discussed. Theodore M. Shapira.

Sautter, H. **Aplasia of the dilator pupillae in Marfan's syndrome.** Klin. Monatsbl. f. Augenh. **114**:449-453, 1949.

Fifty percent of the patients with Marfan's syndrome (arachnodactyly, kyphoscoliosis, dolichocephaly and deformity of the thorax) have abnormal eye findings, mostly in the form of a luxated or subluxated lens. The author draws attention to the examples of miosis and poor response to mydriatics described in the

literature. In order to obtain the anatomic basis for such miosis he examined a piece of iris obtained during cataract extraction in such a patient. He found absence of the dilator pupillae and relatively little pigment in the pars retinae of the iris. Bruch's membrane was also lacking. (2 figures, references.) Max Hirschfelder.

9

GLAUCOMA AND OCULAR TENSION

D'Ombrain, Arthur. **The nature, recognition and treatment of glaucoma.** M. J. Australia **2**:196-200, Aug. 6, 1949.

Clinically there are two main forms of glaucoma, primary and secondary. Primary glaucoma is divided into two groups, acute congestive and chronic. The author divides secondary glaucoma into acute and chronic groups. In an attack of acute glaucoma there is severe pain accompanied by nausea and vomiting, reduction of vision, and the pupil is usually dilated and immobile. The eyeball is engorged and tender, and hard as stone. In chronic glaucoma the main symptoms are a history of rainbow halos, transient attacks of pain and blurred vision and a tendency to bump into objects. The main signs are enlargement of blind spots, cupping of disc and an increase in pressure as measured by a tonometer. Supplementary and provocative tests are the vascular lability test, the water drinking test, the plotting of the fluctuating diurnal curve, dark room test, the caffeine test and the determination of the response to mydriatics. In acute glaucoma morphine relieves pain and secondly contracts the pupil. Local treatment, to convert the condition from an acute to a quiescent or subacute state, consists of eserine sulphate, 1 percent, instilled every one-half hour. If the attack has not subsided after 24 hours, surgery is imperative. In chronic glaucoma the only way to find out the efficiency of miotics in a particular patient is by trial. If tension fails to remain normal and if fields contract, surgery is indicated.

It is the author's opinion that the vasomotor nervous factors are merely contributing or precipitating factors and do not play a significant role in simple glaucoma unless the eye is predisposed to glaucoma by impairment of the trabecular filtering structure. In chronic simple glaucoma the predisposing causes are all forms of impairment of the mechanism of exit and all other causes are merely contributing or precipitating factors.

Theodore M. Shapira.

Kronfeld, P. C. **Further gonioscopic studies on the canal of Schlemm.** Arch. Ophth. **41**:393-405, April, 1949.

Repeated gonioscopic studies under varied conditions were made. Under conditions of normal life the canal of Schlemm contains a colorless fluid. Various experimental procedures cause gonioscopically visible entrance of blood into the canal. Decrease in ocular tension and rises in venous pressure appear to be the outstanding factors that bring on the filling phenomenon. If it has been produced by induction of ocular hypotony, compression of the globe will cause the filling phenomenon to disappear promptly. The insertion of the gonioscopic contact lens may at times cause blood to enter the canal. The observations lend support to the concept that a pressure gradient and, consequently, a continuous flow exists between the canal and the anterior scleral veins. John C. Long.

Meyer, S. J. **Diathermy cauterization of the ciliary body for glaucoma.** Arch. Ophth. **41**: 417-428, April, 1949.

Cyclodiathermy puncture is indicated in cases of glaucoma in which other surgical methods have failed or in which other surgical methods cannot be attempted.

The procedure is indicated in cases of flat anterior chamber, especially after trephination or iridectomy; aphakia, with secondary glaucoma; secondary glaucoma due to prolapse of the iris; primary glaucoma in which the chamber angle is obliterated, and hemorrhagic glaucoma. The author's surgical technique is described in detail. Multiple punctures are made in the sclera with a small diathermy needle in a zone 2.5 mm. wide just above the insertion of the inferior rectus muscle, and extending to within 2 mm. of the insertions of the medial and lateral rectus muscles. The punctures should not be made nearer than 2.5 mm. from the limbus. Operation was carried out in 142 patients, but the histories of only 126 could be obtained. Pain was relieved in 74 percent and tension reduced below 35 mm. of mercury in 33 percent.

John C. Long.

Scheie, H. G. **Goniotomy in treatment of congenital glaucoma.** Arch. Ophth. **42**:266-282, Sept., 1949.

The results obtained from goniotomy in the treatment of 16 eyes (nine patients) with congenital glaucoma are reported. The outcome in these eyes is comparable to the report by Barkan. Goniotomy possesses many advantages over other operations for congenital glaucoma. It seems very effective if done early. A second operation was done only once in the author's series. The chief danger is hemorrhage into the anterior chamber. There is danger of injury to the ciliary body and of producing iridodialysis. Subluxation of the lens must be considered a possibility, and in several of the patients peripheral anterior synechias developed after operation, but these adhesions can be avoided by the postoperative injection of air into the anterior chamber. Scheie attempted to use the goniotomy lens twice in this series of cases but found that it offered no advantages and served only to make the operation more difficult. No late complications have been observed. The operation, therefore, tends to circumvent the objections to the various filtration procedures, such as late infection and cataract. The tension in 11 of 14 eyes with congenital glaucoma was successfully lowered by goniotomy. Goniotomy failed to control the tension in the two eyes of the same patient in which the elevated tension was associated with bilateral port wine nevus of the face and eyelids. All the patients successfully treated have been followed two years or longer.

Ralph W. Danielson.

Schreck, E. **Cilo-anolysis and cilo-cycloanolysis. New operations for glaucoma.** Arch. f. Ophth. **149**:95-141, 1949.

The purpose of these two operations is to lower the ocular tension by permanent closure of one or both of the long posterior ciliary arteries just in front of or just behind the ora serrata. In addition, an electrolytically formed fistula connects the basal iris with the ciliary body. Forty-four eyes have been operated upon and were followed up for 6 to 16 months. The tensions seem to be normalized in at least 75 percent of the cases. Ernst Schmerl.

Sondermann, R. **The pathology of glaucoma.** Klin. Monatsbl. f. Augenh. **114**:458-466, 1949.

The author reaffirms his earlier theories concerning the origin of normal and pathologic intraocular pressure. He regards the intraocular pressure as the result of an increased blood pressure within the uveal veins and capillaries. This increase is due to a narrowing of the channels of exit from the choroid towards the vortex veins within the scleral canal. Loss of elasticity of the sclera in the senile may lead to an increase of venous pressure within the uvea. The safety valve mechanism, represented by the ciliary

body as source and the canal of Schlemm as exit of aqueous is usually poorly functioning in these older patients as a result of sclerosis. Vogt's cyclodiathermy does not attack the formation of aqueous, because it is likely that there was a decrease of aqueous formation previous to the glaucomatous process. Cyclodiathermy results in the opening up of new venous channels through the sclera. This may result in a relief of the venous stasis within the choroid and may accomplish the fall in intraocular pressure. Max Hirschfelder.

Stocker, F. W. **Clinical experiments with new ways of influencing the intraocular tension: II. Use of rutin to enhance the tension-reducing effect of miotics by reducing the permeability of the blood-aqueous barrier.** Arch. Ophth. **41**:429-435, April, 1949.

It is thought that rutin reduces the side effects of miotics, such as the increase in permeability of the blood-aqueous barrier, and thus enhances their efficiency. Of 26 eyes with chronic simple glaucoma, 17 were notably better controlled by miotics after 20 mg. of rutin had been given the patient three times a day for four weeks. In 4 eyes the result was questionable, in 5 the condition did not improve. Rutin is a valuable adjuvant to the treatment of chronic simple glaucoma with miotics.

John C. Long.

10

CRYSTALLINE LENS

Farber, D. N. **Cataract in dystrophia myotonica.** Arch. Ophth. **41**:450-459, April, 1949.

Dystrophia myotonica is a heredofamilial degenerative disease characterized by myotonia and muscular atrophy and by the presence of certain extramuscular signs. The most important of the extramuscular manifestations is cataract, which is to be observed in all cases if carefully looked for. The early lens changes occur in the anterior and posterior cortical regions, close to, but not immediately under, the capsule. In these locations many tiny grayish white opacities are interspersed between iridescent crystals of all hues. Ultimately there is a complete soft cataract with a small nucleus. Cataracts in this disease show the phenomenon of "anticipation," occurring at an earlier age in each succeeding generation. The author describes three cases of dystrophia myotonica with all the characteristic features of the disease, including cataract. The other ocular symptoms found bilaterally in each case were ptosis and loss of orbital fat.

John C. Long.

Moreno, Julio. **Simplified phacoeresis.** Arch. Soc. oftal. hispano-am. **9**:508-524, May, 1949.

Moreno reports a modification of the simple suction instrument designed by Perez Llorca. The platinum suction cup has a curved flange 1 mm. wide inside the edge which is applied to the lens. He also describes a forceps, which he uses for grasping the tendon of the superior rectus, as well as for grasping the iris in making the iridectomy or iridotomy, and a silver spatula for replacing the iris which is made in the form of a lacrimal dilator. The latter is easier to manipulate and safer than the standard spatula. In 104 cataract extractions 96 lenses were extracted in the capsule. (10 figures.)

Ray K. Daily.

Perez Llorca, Jose. **Cataract extraction.** Arch. Soc. oftal. hispano-am. **9**:501-507, May, 1949.

Two technical maneuvers are described. Fixation is done by introducing a silk suture in the episclera at the point desired for fixation and knotting it. This knot is then grasped by the fixation forceps; this avoids pressure on the sclera

and tearing of the conjunctiva. The second maneuver deals with the extraction of the lens, which is done with a small suction apparatus, consisting essentially of a metallic suction canula attached to a firm rubber bulb, similar to the one used with contact lenses. This device is described as simple, safe, easy to manipulate, and effective. (4 figures.)

Ray K. Daily.

11

RETINA AND VITREOUS

Cassady, J. V. **Congenital cyst of the vitreous.** Arch. Ophth. **41**:734-735, June, 1949.

A round cyst was found floating in the middle of the vitreous in the right eye of a boy, aged 9 years. The cyst cast a shadow on the fundus. It moved and floated about with movements of the eye but returned to its original position near the center of the globe when the movement ceased. The apparent pigmentation of the cyst was an illusion. It is seen as a silhouette against the light reflected from the eyeground. These cysts are probably a part of the primitive Bergemeister's papilla or a remnant of the covering of the hyaloid artery. John C. Long.

Damel, C. S. **Macular dystrophy.** Arch. de oftal. d. Buenos Aires **23**:335-359, Nov.-Dec., 1948.

This discussion deals with a family of six individuals suffering from heredomacular degeneration, observed over a period of 21 years. The condition maintained a dominant genetic character not dependent upon consanguinity. It usually begins during puberty and soon after there is an insidious, slow, progressive loss of vision. In the fundus there is great variation in the type and amount of neogenesis of tissue, of hemorrhage, and of whitish exudates. The cases studied were readily classified as inverse pigmentary retinitis punctata albescens, massive pigmentary reaction, massive exudative reaction, Doyne's choroiditis, rosette figuration, or extensive macular involvement. The disease steadily grows worse. (22 figures, references.)

Edward Saskin.

Fischer, Frang. **Macular changes in acute retrobulbar neuritis.** Klin. Monatsbl. f. Augenh. **114**:511-513, 1949.

Of 180 patients with acute retrobulbar neuritis 14 percent had changes in the macula. Small, depigmented spots, retinal edema and irregular pigmentation were found. The edema and pigment irregularities disappeared with recovery. The majority of these patients had multiple sclerosis. Max Hirschfelder.

Geserick, Heinz. **Acute poisoning with methyl alcohol.** Klin. Monatsbl. f. Augenh. **114**:502-511, 1949.

Very broad, white stripes which followed the course of the upper and lower retinal arteries were found in two cases on methyl-alcohol poisoning. They were confined to the region near the papilla and were associated with scotomas emanating from the blind spot. In one patient who recovered, these scotomas were mapped during a period of 19 days. The disturbance is probably of arterial origin, a point which is emphasized by the narrowing of the retinal arterioles in methyl alcohol poisoning. (3 figures.)

Max Hirschfelder.

Gscheidel, Erich. **A hitherto unknown change in the pigment epithelium in the macular area.** Klin. Monatsbl. f. Augenh. **114**:496-502, 1949.

The author observed a bilateral macular lesion among German troops in northern Finland characterized by small, round, bright-red spots and very fine reddish streaks within the macular area which did not affect central vision and which he

ascribes to defects in the pigment epithelium. It was found in all age groups and, as later examinations proved, is not limited to soldiers in certain areas. It was seen in southern German peasants and American and English aviators. (3 colored figures.) Max Hirschfelder.

Hollenhorst, R. W., and Wagener, H. P. **The ocular fundus in relation to operations for hypertensive cardiovascular disease.** Am. J. M. Sc. **218**:225-234, Aug., 1949.

The ophthalmoscopic examination of patients with hypertensive cardiovascular disease should be directed not only toward the presence or absence of hemorrhages, cottonwool patches and edema of the retina and optic disc, but should include a meticulous grading of the degree of arteriolosclerosis, angiospasm, and tonic narrowing of the arterioles. Since the degree of benefit obtained from surgical therapy seems rather definitely to be inversely proportional to the degree of organic retinal vascular change, it is important that ophthalmoscopic examination be included in the studies used for the preoperative evaluation of such patients. They emphasize that no retinal changes are an absolute contraindication to sympathectomy, but the presence of the higher degrees of sclerosis and of retinopathy with papilledema reduces the probability of obtaining a good result.

Theodore M. Shapira.

Mejer, F. **Results of bulbus-shortening operations after Lindner.** Klin. Monatsbl. f. Augenh. **114**:513-523, 1949.

The bulbus-shortening operation of Lindner is indicated in those cases of retinal detachment which have an unfavorable prognosis with the usual methods of detachment surgery. It is not always possible to obtain complete reattachment in these cases, but one frequently obtains considerable improvement in otherwise hopeless cases. Control examinations during the first two postoperative years showed that of 36 patients who had bulbus-shortening operations 8 were completely well, 7 had a stationary remnant of a detached area and in 21 the operation was unsuccessful. The end result was not related to the presence or absence of aphakia or high myopia, but to the structural changes within the vitreous. Shrinkage of the vitreous with formation of strands gives an unfavorable prognosis. In 11 patients the operation was done on the only remaining eye. Some of them had two or three bulbus-shortening operations. In four the operation was completely successful and in three partially successful.

Max Hirschfelder.

Pereyra, L. **Sclerosis of the choroidal vessels and retinal pigmentosis.** Giorn. ital. oftal. **1**:532-542, Nov.-Dec., 1948.

The author observed five cases of sclerosis of the choroidal vessels, both of the hereditary and familial type, associated with central and peripheral tapetoretinal degeneration and believes that the retinal changes are secondary to the lesions of the choroidal vessels. There probably is no single cause of all retinitis pigmentosa. Vito La Rocca.

Reese, A. B. **Heredity and retinoblastoma.** Arch. Ophth. **42**:119-122, Aug., 1949.

It has been well established that there is a strong hereditary tendency in retinoblastoma. The author communicated with the families of 171 consecutive patients with retinoblastoma and received the desired data from 91. In 86 cases both parents were healthy and 60 of the patients had a total of 103 siblings. Only one of the siblings had retinoblastoma. An analysis of these other data indicates that

the likelihood that a second sibling will be affected is less than four percent, and is probably nearer one percent. The author, therefore, does not hesitate to advise healthy parents who have had one child with retinoblastoma to have more children. In the series studied there were five survivors of retinoblastoma who had children of their own. Of their eight children, seven had bilateral retinoblastoma. These figures are sufficiently impressive to the author to interdict the bearing of progeny by all survivors of retinoblastoma. John C. Long.

Tavolara, L. **Pigmentary degeneration of the retina (Lawrence-Moon-Bardet-Biedl syndrome).** Giorn. ital. oftal. **2**:52-58, Jan.-Feb., 1949.

The author describes a case of sectional retinitis pigmentosa in a patient 26 years of age who had disturbances of the genitalia and a tendency to adiposity. The pigment disturbance was limited to the lower nasal quadrant in both eyes with characteristics of an atypical pigmentary degeneration. To the retinal lesions are attributed the alterations of the temporal and upper sections of the visual field. Vito La Rocca.

Vannucchi, V., and Esente, I. **Thrombocytic acroangiothrombosis.** Giorn. ital. oftal. **2**:26-42 Jan.-Feb., 1949.

Recently a new pathologic entity, acroangiothrombosis, was found, which is characterized by grave anemia and piastrinopenia, hemorrhagic diathesis, and involvement of the nervous system. In a patient with splenomegaly and bilateral thrombotic retinopathy the authors made a tentative diagnosis of thrombocytic acroangiothrombosis but an unequivocal diagnosis of this disease can only be based upon a histologic study. The authors point out the diagnostic value of a careful examination of the eyeground in every case of hemorrhagic diathesis.

Vito La Rocca.

12

OPTIC NERVE AND CHIASM

Goldsmith, J. **Neurofibromatosis associated with tumors of the optic papilla.** Arch. Ophth. **41**:718-729, June, 1949.

A case of bilateral tumor of the optic nerve, involving the papilla and associated with neurofibromatosis in a 26-year-old white man is reported. Unusual associated findings were a neurofibromatous growth in the apex of the righ lung, bilateral acoustic neuroma, mental retardation and medullation of the retinal nerve fibers. Other ocular lesions associated with neurofibromatosis are described. It is suggested that all patients with neurofibromatosis be subjected to a critical ophthalmologic examination.

John C. Long.

Radnot, M. **Cavernous degeneration of the optic nerve.** Arch. d'opht. **9**:454-457, 1949.

Radnot reports the case of a woman, 59 years of age, whose right eye was removed because of melanoma of the iris with secondary glaucoma. Microscopic examination showed a flat excavation of the optic nerve with severe atrophy of nerve fibers. The central vessels were dilated and surrounded by a lymphocytic infiltration. In the nerve there was cavernous degeneration with the spaces filled sometimes with transudate, sometimes with debris. The author reviews the literature on cavernous degeneration and notes the infrequency of the lesion. He refers to his demonstration of this type of degeneration in only three of 53 eyes with uveal tumor and expresses the belief that increase in the ocular tension plays an important causative role.

Phillips Thygeson.

13

NEURO-OPHTHALMOLOGY

Adler, F. H., Austin G., and Grant, F. C. **Localizing value of visual fields in patients with early chiasmal lesions.** Arch. Ophth. **40**:579-600, Dec., 1948.

Some information as to the position of a lesion in relation to the chiasm may be gained by an analysis of the early field changes and nine cases are reported which show the changes that have the greatest localizing value. Bitemporal hemianopic scotoma with or without bitemporal contraction suggests a lesion that encroaches on the posterior surface of the chiasm, most probably a craniopharyngioma. Loss of one temporal field with loss of the opposite superior temporal quandrant suggests a tumor on the side of the greater field loss at the anterior end of the chiasm under the optic nerve and is characteristic of pituitary adenomas. Binasal hemianopsia that is more complete on one side than the other indicates pressure at the lateral aspect of the chiasm on both sides. The lesion is probably on the side with the greater field loss, and the defect in the other side of the field is ascribed to pressure of the internal cartoid artery or to pressing of the nerve against the bony wall of the optic foramen. Bitemporal hemianopic fields with bizarre scotomas indicate a tumor at the anterior end of the chiasm which probably involves the nerve on the side of the scotoma. John C. Long.

Austin, G. M., Jr., Lewey, F. H., and Grant, F. C. **Studies on the occipital lobe: significance of small areas of preserved central vision.** Arch. Neurol. and Psychiat. **62**:204-221, Aug., 1949.

Six cases of left occiptal lobectomy are presented which show preservation of central vision ranging from 0.25 to 1.5 degrees. The various theories used to explain macular sparing are discussed. The authors feel that there is no evidence to support the theory of bilateral macular or foveal representation. They found the same degree of macular sparing in eight patients with chiasmal lesions. The preservation of central vision of less than 2 degrees can be ascribed to the slight physiologic variation in fixation, to the situation and extent of the lesion in the optic pathways, as well as to a minimal eccentricity of the fovea. (6 figures, 2 tables.) H. C. Weinberg.

D'Ermo, F. **Two cases of crocodile tears associated with Turk's syndrome.** Boll. d'ocul. **28**:273-288, May, 1949.

D'Ermo observed two patients, children, 5 and 16 years of age, with the Turk-Stilling syndrome which consists of congenital "crocodile tearing" and inhibited abduction with retraction of the eyeball. The tearing was elicited by chewing acid, bitter, sweet, or salty food. The two anomalies cannot be explained etiologically by a single lesion. For treatment of the most inconvenient lacrimation, the author recommends removal of the lacrimal gland. (3 photographs of patients, 1 anatomical drawing, references.) K. W. Ascher.

Di Marzio, Quirino. **Optochiasmatic arachnoiditis.** Riv. oto-neuro-oftal. **24**: 119-135, March-April, 1949.

This type of arachnoiditis is characterized clinically by visual disturbances with campimetric and papillary changes, more or less rapid decrease of vision and tendency to total blindness, and, anatomically, by inflammatory thickening of the arachnoid of the chiasm and the optic nerves. For the differential diagnosis an important diagnostic point is the brusque starting of symptoms and rapid evolution and progressive lowering of the vision. The disc, which in the beginning shows a papillary edema, becomes slowly atrophic. Rarely the disease

may start with instantaneous blindness or it may have a slow course. In some cases there is a remission of symptoms or relapses may follow, terminating in optic atrophy. In cases of known etiology causal therapy is indicated such as intravenous arsenobenzol and iodine, radiotherapy, vitamin D_2 in shock doses and operations for sinusitis and mastoiditis. Intracranial surgery, if used in time, stops the progress of the disease in the majority of the patients.

Melchiore Lombardo.

Graveson, G. S. **The tonic pupil.** J. Neurol. Neurosurg. Psychiat. **12**:219-230, Aug., 1949.

A résumé of the salient facts found in fifteen patients with tonic pupils is given in the two tables. In all cases there was tonicity in response to light, convergence, or accommodation. Two types of tonic pupil are described. The first is the fixed type in which the defect is unilateral and and the affected pupil is larger than normal, irregular in shape, and totally unresponsive to light or convergence. The pupil contracts slowly and relaxes slowly with accommodation. In the second type the pupil is irregular in shape or position, and dilates very slowly after convergence. The disturbance may be unilateral or bilateral, the pupil may be of any size, and the light reflex may be normal or absent.

The physiopathologic disorder which may be the cause of the tonic pupil is first a disturbance of conduction in pupillomotor fibers and secondly an alteration in the chemical changes resulting from stimuli at the myoneural junction. The conduction defect probably occurs in the short ciliary nerves. A delay in the destruction of acetyl choline at the myoneural junctions prevents normal relaxation and results in slowness of dilatation after the pupil contracts.

H. C. Weinberg.

Jones, I. S. **Anisocoria.** Arch. Ophth. **42**:249-253, Sept., 1949.

The value of anisocoria as a diagnostic sign has been limited by reports of normal or physiologic anisocoria in as high as 40 percent of all patients. Lowenstein's pupillographic method has eliminated a large number of cases of these so-called physiologic anisocorias through detailed cinematographic analysis under both static and dynamic conditions. In order to realize the potentialities of this method, and in order to place the proper value on the finding of anisocoria, it is necessary to delimit sharply that which may be physiologic from that which is pathologic. Toward this end the present study was undertaken.

The average difference between the pupils in the dark-adapted patient was 0.21 mm. Only one subject showed an amount sufficient to be detected reliably by ordinary observation. The change in the amount of anisocoria was approximately the same for all levels of illumination, namely, 0.02, 12 and 92 foot candles. However, the illuminated pupil did not constrict more than the unilluminated pupil. It appears that uniform illumination of one eye within the limits of time and intensity of this study may be disregarded as a cause of anisocoria. It should be emphasized that these studies were confined to illumination of the central portion of the retina and did not include stimulation of the temporal or nasal part of the retina.

Ralph W. Danielson.

Kreibig, W. **Neurofibromatosis of the eye.** Klin. Monatsbl. f. Augenh. **114**:428-449, 1949.

The ocular involvement in neurofibromatosis is described and illustrated by means of four cases. The author accepts the Masson-Feyrter theory concerning the neurogenic origin of nevus cells and ovoid bodies. Hydrophthalmus due to

malformation of the chamber angle was present in all four patients. The significant lesion was within the choroid. There was a great increase of pigmented cells, variable in form from spindle to round cells. Some of them spread diffusely throughout the tissue while others were clumped together in little islands. There was also an increase in all nervous elements, medullated and nonmedullated nerve fibers as well as ganglion cells. Laminated structures (ovoid bodies) which are normally found within the skin and are pathologically seen in pigmented nevi were a typical finding in the choroid. There are no epithelial tissues within the uvea and these bodies must of necessity be of neurogen origin. It is plausible to assume that the pigmented cells are also of neurogenic origin. The author believes that histologic findings in ocular neurofibromatosis provide a link between the pigmented tumors of the skin and the melanosarcomas of the choroid. The neurogenic origin of all pigmented tumors seems to receive further confirmation from the appearance of cell structures in ocular neurofibromatosis which are similar to structures found in normal or pathologic skin. (20 figures, references.)

Max Hirschfelder.

Larmande, A. **Acute nuclear ophthalmoplegias and vitamin B_1 deficiency.** Arch. d'opht. **9**:347-352, 1949.

In a review article Larmande summarizes the evidence which establishes conclusively that vitamin B_1 deficiency is capable of producing an acute nuclear ophthalmoplegia. The deficiency may be due to inadequate intake, as in World War II prisoners of the Japanese, or to chronic disturbances of the digestive system, as in cancer, gastritis, hepatitis, diarrhea, and vomiting. It occurs frequently in chronic alcoholism as a result of three related mechanisms, namely, deficiency of intake, deficiency of assimilation due to gastritis, and deficiency of utilization due to the toxic effect of the alcohol. The disease may occur during pregnancy when four or five times the normal amount of the vitamin is required. The essential lesion is a hemorrhagic polioencephalitis and the use of thiamin hydrochloride in large therapeutic doses is indicated. This medication has profoundly influenced the clinical course of the disease. The author emphasizes the frequency of multiple vitamin deficiencies.

Phillips Thygeson.

Mooney, A. J., and McConnell, A. A. **Visual scotomata with intracranial lesions affecting the optic nerve.** J. Neurol. Neurosurg. Psychiat. **12**:205-218, Aug., 1949.

The seven cases reported show how scotomata can be produced by pressure that obstructs the blood supply of the intracranial or intracanalicular portions of the optic nerves. Central scotomata may appear early because the septa in the axial portion of the nerve, where the papillo-macular bundle is situated, are thinner and scarcer than elsewhere. The nutrition of the bundle is therefore less abundant and more easily disturbed in the intracranial and intracanalicular portions by compression of the ophthalmic artery. The authors review some of the current theories which are used to explain the appearance of central scotomata with expanding intracranial lesions. It is probable that pressure on the intracranial portion of the ophthalmic artery is very often the direct cause of scotoma and especially central scotoma. (34 figures.)

H. C. Weinberg.

Rubino, Alfio. **The "meningo-endocranioses" in ophthalmology.** Riv. oto-neuro-oftal. **24**:1-89, Jan.-Feb., 1949.

The meningo-endocranioses, which are for the most part chronic inflammatory

processes in the meninges, particularly the pia-arachnoid, are discussed extensively from the viewpoint of every discipline of medicine from neurology and endocrinology to radiology and ophthalmology. Symptoms, pathology and etiology are thoroughly considered. For the ophthalmologist the manifestations of importance are fundus lesions that result from disturbanes of the circulatory system of the eye and disturbances in the field of vision. Melchiore Lombardo.

Stansbury, F. C. **Neuromyelitis optica (Devic's disease).** Arch. Ophth. **42**:292-335, Sept., 1949 and **42**:465-501, Oct., 1949.

This review of the literature and report of cases is extensive. In view of the new theory of the common identity of the demyelinating diseases, neuromyelitis optica assumes a new importance. It has a much greater mortality rate than multiple sclerosis and therefore affords more material for pathologic study. Five cases of neuromyelitis optica have been diagnosed in the Columbia-Presbyterian Medical Center in the past twenty years; the clinical records and the pathologic findings are presented. This disease occurs commonly between the ages of 30 and 50 years, more often in females and is not limited to the white race. The initial symptoms are referable to the visual system in one-half the cases and to the spinal cord in the rest. Severe binocular loss of vision is characteristic. The rapidly ascending nature of the myelitis is the only characteristic neurologic finding. Remissions occur in about one-half the cases. The patient frequently dies in the first three months of his illness.

Histologically, the disease is characterzed by demyelination of nerves, destruction of axis-cylinders, mild astrocytosis, pronounced microglial proliferation, perivascular infiltration of white blood cells, proliferation of capillaries and, sometimes, gross cavitation. The hypothesis of the common etiology of the demyelinating disease group rests mainly on the demonstration of a similar pathologic process. However, the demonstration of similar, or even identical, pathologic changes does not prove the existence of a common cause. Ralph W. Danielson.

Wartenberg, Robert. **"Inverted Marcus Gunn phenomenon" (so-called Marin Amat syndrome).** Arch. Neurol. and Psychiat. 60:584-596, Dec., 1948.

The author briefly reviews the literature and the cases reported which show the syndrome in which the eyelid is closed when the patient opens the jaw. This is the inverted Marcus Gunn phenomenon. In the true Marcus Gunn phenomenon the eyelid is lifted up when the mouth is opened.

The cases reported and analysed show that this inversion of the Marcus Gunn phenomenon occurs after peripheral facial palsy. The orbicularis oculi muscle contracts when the lower facial muscles are stimulated and not necessarily when the mandible moves. The closure of the eye is the commonest of all the associated movements among the facial muscles seen after peripheral facial palsy.

The concept of the Marin Amat syndrome as an inverted Marcus Gunn phenomenon and as a trigeminofacial associated movement does not bear critical analysis. It is based on misconception and is not justifiable. (4 figures.)
H. C. Weinberg.

Weinstein, E. A., and Dolger, H. **External ocular muscle palsies occurring in diabetes mellitus.** Arch. Neurol. and Psychiat. **60**:597-603, Dec., 1948.

The authors describe the ocular palsies found in 14 diabetic patients who showed

evidence of vascular damage. Seven patients had a disturbance of function of the third nerve, six had paralysis of the sixth nerve and one had a combined third and sixth nerve palsy.

The patients with third nerve palsies had varying degrees of dissociation which suggests that the lesion is in the ventrocaudal portion of the oculomotor nucleus or its emergent rootlets, especially when there is sparing of pupillary function and downward movement. In two cases there was a reversal of the lid closure phenomenon and a paralysis of pupillary action on convergence in the contralateral otherwise unaffected eye. All the patients showed evidence of generalized vascular damage with retinal hemorrhages so that it is not necessary to postulate a "toxic neuritis" or a vague metabolic error to account for these palsies. The neurologic lesion is not related to the age of the patient or the severity of the diabetes but to the duration of the disease and consequently on the amount of vascular damage.

H. C. Weinberg.

Zbikowski Balbontín, Enrique. **Marcus Gunn phenomenon in a child.** Arch. Soc. oftal. hispano-am. **9**:666-669, June, 1949.

An infant, three days old, was seen with a partial paralysis of the left levator of the lid, redness and local hyperthemia of the left side of the face, and miosis of the left pupil. The picture was regarded as a Claud Bernard Horner syndrome caused by compression of the neck during birth. Within a month the skin symptoms and miosis disappeared, and the ptosis improved, covering only half of the palpebral fissure. The Marcus Gunn phenomenon suddenly appeared soon afterwards. The elevation of the drooping lid with movements of the mandible exceeded that of the normal side and the ptosis increased while the infant was laughing. The author believes that the primary paralysis of the sympathetic was the stimulus for the development of the abnormal nerve association responsible for this phenomenon. The literature on the pathogenesis of this anomaly is reviewed, and the author concludes that the phenomenon is due to the existence of peripheral motor association fibers between the motor branch of the fifth and the oculomotor nerves. Probably many cases regarded as congenital are actually acquired early in life as a consequence of disease.

Ray K. Daily.

14

EYEBALL, ORBIT, SINUSES

Marino, Héctor. **Orbitopalpebral reconstruction; sinew ingraft by injection of cartilage.** Arch. de oftal. d. Buenos Aires **23**:375-379, Nov.-Dec., 1948.

Severe orbital trauma, with loss of the globe, is usually associated with sequential orbitopalpebral deformity which frequently requires more than a single surgical correction. In this type of reconstruction the author suggests the use of fragmented pieces of spongy iliac bone or costal cartilage from the same individual, cadaver costal cartilage, or even heterologous bovine cartilage. He advises fragmentation before implanting because of the greater ease in molding, and prefers an incision in the brow when possible. In order to increase the resistance of the lower lid necessary to retain the prosthesis he employs a piece of toe tendon placed in the free border of the lid. (3 figures.)

Edward Saskin.

Piquet, J., Ducrocq, R., and François, P. **Orbital and ocular complications of suppurative sinusitis.** Arch. d'opht. **9**:176-200, 1949.

The authors report a comprehensive study of the ophthalmologic complica-

tions of nasal sinus disease. These they divide into suppurative and nonsuppurative types and note that nonsuppurative complications, such as orbital and palpebral edemas, are rare in the adult but do occur in closed empyemas. In the infant, however, they are common, particularly during attacks of coryza or influenza associated with acute ethmoiditis or fronto-ethmoiditis. Lid swellings in these cases are more common than orbital edemas. Of epidemiologic interest was the finding that these complications tend to occur in the winter months and are much more frequent in certain winters.

The suppurative complications include subperiosteal abscess, palpebral abscess, or cellulitis of the orbit. The inciting sinusitis may be acute or latent and the authors report 26 cases in which latency was an outstanding feature. In one case rhinologic examination was negative, the ethmoids were clear to X-ray examination, and the microscopic lesions of the ethmoid cells were insignificant. In 35 cases of frontal sinusitis with perforation in adults there were 15 acute cases, 11 cases of chronic sinusitis with acute exacerbations, and 9 cases of sinusitis of sluggish evolution without marked inflammatory signs. In two cases of frontal sinus empyema perforation occurred without the least evidence of acute nasal infection.

The authors describe the bacteriology of 33 cases and note that the staphylococcus was in general the most dangerous germ but that death occurred in three cases in which the infecting organisms were staphylococci, streptococci, and diphtheria bacilli respectively. They describe the anatomic pathways by which infection passes into the orbit.

The eye complications noted were chemosis, loss of motion of the globe due to brawny infiltration of the orbital tissues, uveitis, thrombosis of the retinal vessels, oculomotor paralysis, and optic neuritis. Phillips Thygeson.

Schoenfelder, Richard. **A rare case of injury of the left maxillary sinus and the orbit.** Klin. Monatsbl. f. Augenh. **114**:452, 1949.

A boy fell into the root-stock of a shrub. There was a fistula at the inner lower canthus and the eye was pushed outward. Eight wooden splinters had been pushed into the maxillary sinus. After their removal through an opening in the region of the canine tooth the eye returned to normal position and the wound healed uneventfully.

Max Hirschfelder.

Schwarz, M. **Factors in spontaneous involvement of lids and orbit in diseases of the sinuses.** Klin. Monatsbl. f. Augenh. **114**:535-541, 1949.

Between 70 and 80 percent of inflammatory or neoplastic swellings in the orbit are of nasal origin. Inflammatory conditions are five times as frequent as benign tumors and three times as frequent as malignant tumors. The majority of the inflammatory palpebral and orbital swellings due to sinus disease are caused by acute purulent infections. Only one-fifth can be ascribed to chronic sinusitis which is often accompanied by a rarefying osteitis. Perivascular, perineural and thrombophlebitic spread of the infection is noted. Tumors invade orbit and lids by bony channels with osseous infiltration in the case of malignancy. The frontal and ethmoid sinuses are the most frequent primary seat of inflammatory palpebral and orbital spread, while the maxillary sinus is only rarely the offender. Gravity may be the reason for this phenomenon. Poor drainage through the ductus nasofrontalis or through the ostias of the ethmoid cells favor accumulation of purulent matter. The author stresses

the inherited susceptibility of the mucous membrane of certain families to infectious processes. It is the inherited type of reaction of the mucous membranes which dominates the picture of sinusitis. The virulence of the invading bacteria is only of secondary importance.

Max Hirschfelder.

Strandberg, Brynjulf. **Cephalocele of posterior part of orbit.** Arch. Ophth. **42**:254-265, Sept., 1949.

By cephalocele of the posterior part of the orbit is understood cerebral hernia arising from the middle cerebral fossa and penetrating into the posterior part of the orbit behind the bulbous oculi, through a preformed or new opening in the wall of the orbit. In the present survey of 31 cases, only those have been included in which the symptomatology was characteristic and in which reontgenologic or postmortem examination of the cranium established the diagnosis.

The most frequent ocular symptom of cephalocele of the posterior part of the orbit is a slowly developing, unilateral exophthalmos, which appears chiefly in younger persons and, in the majority of cases, pulsates synchronously with the pulse and is reducible by pressure on the bulbous, usually without accompanying cerebral symptoms but sometimes associated with vertigo and nausea. The exophthalmos may change in relation to the cerebrospinal pressure, whereas the pulsation in the majority of cases remains unaffected by compression of the carotid artery on the affected side. The eyeball is displaced, most frequently downward and laterally, but in few cases downward and medially if the deficiency is located in the lateral wall of the orbit. Movement of the eyeball is hampered, the degree depending on the size of the encephalocele. There is a palpable, soft elastic tumor in the orbit. There is edema of the eyelids, most frequently of the upper and in some cases of the lower lid. Ptosis, reduced vision and microphthalmos must in all likelihood be regarded as due to defective development, in the same manner as are the skeletal deficiencies, rather than as secondary phenomena; further, there may be diplopia, central changes in the form of venous congestion, incipient papilledema and coloboma of the optic nerve, when the hernial opening of the cephalocele is formed by an enlarged optic foramen. In isolated cases there are changed visual field, bruit, reduced tension (observed only in cases with concurrent microphthalmos) and nystagmus.

Ralph W. Danielson.

Vail, Derrick. **Exophthalmos.** Postgrad. Med. **5**:439-450, June, 1949.

This article was prepared for The Schneider Foundation Eye Presentation, and covers the subject of exophthalmos in all phases. Attention is called to the distinguishing features between apparent and true proptosis. The author divides proptosis into monocular and binocular types. Monocular proptosis is subdivided into four categories: rapid proptosis with edema of the lids, gradual proptosis without edema, unilateral proptosis with central displacement, unilateral proptosis with lateral displacement. Each category is discussed and the causes enumerated. Photographs and case histories are presented to illustrate the various types

Donald T. Hughson.

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EYELIDS, LACRIMAL APPARATUS

Caballero del Castillo, D. **Our suture for the nasal and lacrimal mucosa in dacryocystorhinostomy.** Arch. Soc. oftal. hispano-am. **9**:532-533, May, 1949.

The excellent illustrations show that a double suture introduced through the

upper skin wound approximates the lining of the lacrimal sac to the mucous membrane flap from the nose, and is brought out through the skin of the lower end of the incision. Both ends are tied over beads. There are no buried sutures, and the sac is attached to the superficial skin layers, so that it cannot be compressed backward and create subsequent obstruction. (6 figures.) Ray K. Daily.

Hoang-Xuan-Man. **A variant of the Motais ptosis operation: the Dickey procedure. Personal observations on its use. History of operations in which the superior rectus is substituted for the levator.** Arch. d'opht. **9**:441-453, 1949.

The author considers the Dickey operation one of the best procedures for the correction of ptosis. In his hands it gave excellent and constant results. It proved to be ideal when the action of the levator was nil but the action of the superior rectus normal. It was also useful when the levator function was not completely abolished. It had decided advantages over the Motais procedure because of its lack of mutilation of the superior rectus. The technique of the operation was facilitated by the use of preserved fascia lata.

Phillips Thygeson.

Steckler, M. I. **Operations for blepharoptosis.** Arch. Ophth. **42**:283-291, Sept., 1949.

The author outlines the various operations for ptosis. Before an attempt at surgical correction is made, the following data should be obtained: vision in each eye and the presence of amblyopia, diplopia or fusion; the sensibility of the cornea, as an estimate of its ability to withstand exposure; the vertical width of the palpebral fissure when looking straight forward, up, and down; estimation of the strength of the elevator power of the muscles of the eyelid by comparing the above measurements of the palpebral fissure with similar ones taken when the frontalis muscle is prevented from acting and corrugates the forehead, with the measurements when the brow is depressed by the fingers of the observer; exophthalmometric reading, if proptosis is suspected; extraocular motility of each eye, especially that of the superior rectus muscle, and the fields of fixation, and the effect of cocaine on the smooth muscle of the lid.

Steckler favors the Dickey operation because the corrected height of the lid can be depended on to remain where it is fixed at the operating table, the operation is not difficult to perform, the superior rectus muscle is not detached from the globe and the whole muscle lends itself to the support of the lid, and there is a minimum chance of any sutures pulling loose. A wide palpebral fissure, or one resembling the unaffected side, may be secured, the fissure resembles the normal elliptic one, and the lid fold is usually satisfactory. The lid follows the eye in its vertical movements. There is no diplopia of any importance in cases of unilateral ptosis provided the superior rectus of the affected side is normal. The operation can be undone simply by everting the lid and cutting one arm of the fascia.

Ralph W. Danielson.

NEWS ITEMS

Edited by Donald J. Lyle, M.D.
601 Union Trust Building, Cincinnati 2

News items should reach the editor by the 12th of the month but, to receive adequate publicity, notices of postgraduate courses, meetings, and so forth should be received by the editor at least three months before the date of occurrence.

Death

Dr. Andrew Rados, Newark, New Jersey, died September 20, 1949, aged 61 years.

Announcements

Slitlamp and gonioscopy course

A course in the practical application of the slit-lamp microscope and newer methods of gonioscopy will be given by the department of ophthalmology of the Montefiore Hospital, Pittsburgh, Pennsylvania, under the direction of Dr. Harvey E. Thorpe and associates. A course on the management of intraocular foreign bodies will be included.

Instruction will begin on Monday, February 27th, and will continue for four days through March 2nd. The class will be limited to 25 physicians to facilitate examination of clinical material.

Further information may be obtained from the committee on graduate education, Allegheny County Medical Society, 225 Jenkins Building, Pittsburgh 22, Pennsylvania.

Stanford conference

The Stanford University School of Medicine will present a postgraduate conference in clinical ophthalmology from March 27 through March 31, 1950. Registration will be open to physicians who limit their practice to the treatment of diseases of the eye or eye, ear, nose, and throat. In order to allow free discussion by members of the conference, registration will be limited to 30 physicians.

Instructors will be Dr. A. Edward Maumenee, Dr. Dohrmann K. Pischel, Dr. Jerome W. Bettman, Dr. Earle H. McBain, and Dr. Arthur J. Jampolsky.

Programs and further information may be obtained from Office of the Dean, Stanford University School of Medicine, 2398 Sacramento Street, San Francisco 15, California.

Miscellaneous

Research Study Club Course

The 19th annual midwinter course sponsored by the Research Study Club is being held in Los Angeles, January 15th to 27th. Dr. Conrad Berens, director of the Ophthalmological Foundation of New York, and his associate, Dr. Raymond E. Meek, and Dr. Percy E. Ireland, head of the department of ophthalmology, University of Toronto, and his assistant professor, Dr. Joseph A. Sullivan, are among the speakers. Dr. Meyer Wiener is giving a course in surgery of the eye.

Eye-Bank and research center opened

Through the efforts of representatives of the Lions Clubs of Western New York and a committee of the Erie County Medical Society, the Buffalo Eye-Bank and research laboratory are being opened in the University of Buffalo School of Medicine.

South American Eye-Bank

Announcement has been received that an Eye-Bank has been founded in Rio de Janeiro. Research studies in keratoplasty and other branches of ophthalmology will be conducted by this organization.

Societies

Brooklyn meeting

At the 110th regular meeting of the Brooklyn Ophthalmological Society on December 15th, Dr. Frederick H. Theodore, by invitation, discussed "Office bacteriology," during the instruction session. Dr. John H. Dunnington, by invitation, spoke on "Re-operations in glaucoma," and Dr. Harvey Thorpe, by invitation, on "The management of intraocular foreign bodies."

Dr. Mortimer A. Lasky is president of the society; Dr. Louis Freimark, secretary-treasurer; and Dr. George A. Graham, associate secretary-treasurer. Presented for membership at this meeting were: Dr. Leo Esbin, Dr. Milton Welt, and Dr. Charles Stern.

Massachusetts Alumni meet

On November 15th and 16th, the annual meeting of the Massachusetts Eye and Ear Alumni Association was held at the Massachusetts Eye and Ear Infirmary, Boston.

Each morning was occupied with a surgical clinic. During the first afternoon session, the following papers were presented: "Bilateral delayed detachment of the choroid following cataract extraction," Dr. Henry F. Allen; "Certain ocular developmental defects," Dr. Parker Heath; "Unilateral internuclear ophthalmoplegia," Dr. William Smith, Dr. David G. Cogan, and Dr. Charles S. Kubik; "Chemistry of the ocular lens: I. Synthesis of glutathione in the normal and cataractous lens," Dr. V. Everett Kinsey and Mr. Frederic C. Merriam. Dr. Edwin B. Dunphy presided at this session.

Dr. Benjamin Sachs, presiding at the first evening session, presented Dr. Albert E. Sloane who spoke on "A simple device for the clinical management of certain binocular functions"; and Dr.

Edwin B. Dunphy who spoke on "Idiopathic hyperlipemia and its ocular complications."

Papers presented during the afternoon of the second day were: "Autogenous vaccine in the treatment of chronic staphylococcal infections of the eye," Dr. David H. Scott and Miss Anita B. Mangiaracine; "The chemistry of aqueous humor and its significance with respect to osmotic pressure and the Donnan effect," Dr. V. Everett Kinsey; "Report on tetra-ethyl-pyrophosphate," Dr. W. Morton Grant; "Retinal detachment with aphakia," Dr. Charles Schepens; "Benign cyst involving the orbit," Dr. Garrett L. Sullivan; "Beta radiation: Indications, technique, and results," Dr. Brendan D. Leahey; "Some experiences with surgery in a mental institution," Dr. H. Frederick Stephens and Dr. Linus A. Sheehan. Dr. F. H. Verhoeff presided at this session.

Reading program

"Retrobulbar neuritis," presented by Dr. John H. Kupp of Palmerton, Pennsylvania, was the ophthalmic subject discussed at the 98th meeting of the Reading Eye, Ear, Nose, and Throat society.

Michigan postgraduate course

The Department of Postgraduate Medicine of the University of Michigan Medical School announces the annual conference in ophthalmology for qualified physicians, April 24, 25, and 26, 1950, to be given at the Horace H. Rackham Graduate School Building, Ann Arbor, Michigan, under the direction of the Department of Ophthalmology.

Guest lecturers will be Dr. John B. Hitz, Milwaukee; Dr. Herman Elwyn, New York; Dr. Albert E. Sloane, Boston; Dr. Paul L. Cusick, Detroit; and Dr. Kenneth C. Swan, Portland. Resident lecturers will be Dr. F. Bruce Fralick, Dr. Harold F. Falls, and Dr. John W. Henderson.

Complete program and details will be mailed upon request addressed to Dr. Howard H. Cummings, chairman, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Michigan.

Orthoptic training course

The American Orthoptic Council is announcing the third annual training course for orthoptic technicians. This course was previously given in Maine in 1948 and in Boston in 1949. The current course will begin in Boston on July 5, 1950. The didactic portion of the course will last through August 30, the tuition fee being $150, and room and board, $100.

The practical portion of the course will be given in various teaching clinics and offices throughout the country during the succeeding year. Nationally known ophthalmologists and certified orthoptic technicians will aid Dr. Walter B. Lancaster with the didactic instruction. Scholarships for worthy students may be available.

Contact the office of the American Orthoptic Council, 1605 22nd Street, N.W., Washington 8, D.C., for further information concerning the course. Deadline for receiving applications is July 1, 1950.

Eye-Bank established in Atlanta

The Clay Memorial Eye Clinic and Emory University School of Medicine through the William L. Crawley Fund have established an Eye-Bank at the Grady Memorial Hospital, 36 Butler Street, S.E., Atlanta 3, Georgia. The facilities of the Eye-Bank are available, without charge, to ophthalmologists and coöperating hospitals throughout the Southeast and any other region of the country.

Local transportation for the Atlanta area is provided by the Atlanta Chapter of the American Red Cross Motor Corps, and regional transportation is provided through the Capital, Delta, Eastern, and Southern Airlines. These Airlines have offered their facilities without any cost.

Any information regarding the function of the Eye-Bank may be obtained from the Eye-Bank, Clay Memorial Eye Clinic, 72 Armstrong Street, S.E., Atlanta 3, Georgia.

Egyptian society

The annual meeting of the Ophthalmological Society of Egypt, to be held at the Memorial Ophthalmic Laboratory, Giza, Egypt, on March 15th and 16th will be devoted to a symposium on "Sympathetic ophthalmia." All medical practitioners, as well as ophthalmologists, are invited to attend.

Personals

Dr. Arthur J. Bedell, Albany, New York, presented the fourth William Hamlin Wilder Memorial Lecture of the Institute of Medicine of Chicago, at the Palmer House, Chicago, on October 14th. The subject of Dr. Bedell's illustrated lecture was "Medical ophthalmology: A Kodachrome demonstration of fundus photographs of diabetes, hypertension, nephritis, optic neuritis, and choked disc."

Dr. Jonas S. Friedenwald, Baltimore, presented the Mark J. Schoenberg Lecture at the New York Academy of Medicine on December 5th. The subject of Dr. Friedenwald's address was "Some problems in the diagnosis and treatment of glaucoma." The Schoenberg lecture is sponsored jointly by the New York Society for Clinical Ophthalmology and the National Society for the Prevention of Blindness.

Dr. Charles A. Crockett has been appointed assistant in ophthalmology at the University of Kansas School of Medicine.

Dr. Friend A. Cross, Scranton, Pennsylvania, has resigned as chief of the ophthalmological service of the Scranton State Hospital after 41 years of continuous service to the hospital.

Dr. John H. Dunnington, New York, presented the Sanford R. Gifford Lecture before the Chicago Ophthalmological Society on January 16th. The subject of the address was "Healing of cataract incisions."

The National Society for the Prevention of Blindness has announced the appointment of John L. Fortson as director of public relations.

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